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LETHAL MIDLINE GRANULOMA; IS IT A PATHOLOGICAL ENTITY?*

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The dramatic clinical picture of progressive ulceration and tissue destruction of the nose and palate, until the whole face may have been eaten away, has been of great interest and study since it was first described by McBride in 1896. The seemingly relentless course of the destruction, in spite of all therapeutic attempts, leaves a profoundly unpleasant and helpless impression found in few other conditions.

At first considered rare, more cases have been reported as the condition has become recognized with greater frequency. Subsequent observers have added to the variety of nomenclature as well. It would seem that arriving at an absolutely uniform name would not be as important as establishing exact criteria which will define the disease.

This study was stimulated by observation of our own cases of lethal midline granuloma and those of colleagues and institutions in our area. In addition, we reviewed the case histories under this heading at the Los Angeles County Hospital since the inception of this institution's disease classification system. We believe that too often a fatalistic attitude has been adopted because of the discouraging prognosis presented by this disease in the past. This has been responsible for paralysis of action, and has served to overlook other con-

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ditions which may be masking as lethal mideline granuloma, and where available specific therapy could be life saving.

From the evidence available which will be presented, it is doubtful whether lethal midline granuloma has the pathological characteristics of a pathognomonic disease. The question, then, may be logically posed whether it should continue to be regarded as a pathological entity. It is our purpose to review the salient features of this condition and to appraise critically the pathogenesis and pathological diagnosis in the light of current concepts in the literature and of our personal experience.

Historically, the first case of progressive ulceration of the nose which ended fatally was recorded by Peter McBride[1] in 1896 in the *Proceedings of the Laryngological Society of London*, under the title, "Case of Rapid Destruction of the Nose and Face." No further reports appeared in the literature until 1921 when Woods reported two cases under the name of "malignant granuloma of the nose." A small number of other cases followed in the English literature, notably by McArthur[3] under the same title, and in the French literature in 1929 under the name of "sacro-lupus pernio," by Chatelier.[4] In 1933 there appeared a comprehensive paper on the subject by Stewart,[5] to which reference is made by most of the succeeding authors in the field. He called it "progressive lethal granulomatous ulceration of the nose." Williams,[6] in his excellent study of present views on the subject, termed it "lethal granulomatous ulceration of the midline facial tissues."

Other terms applied to this entity include: "granulomatous ulcer of the nose and face" (Hoover[7]); "chronic granulomatous ulcer of the nose of unknown cause" (Isbell[8]); "chronic infectious granuloma of the nose" (Lierle[10]); "osteomyelitis necroticans" (Rasmussen[12]); "gangrenous osteomyelitis of the paranasal sinuses (Lewy[11]); and "mutilating granuloma" by Wood[13] which, incidentally, was the first American case reported.

Terms such as osteomyelitis or malignant reticulosis, mesenchyoma and others, which refer to specific inflammatory or neoplastic conditions should, it would seem, better be left out,

since this disease does not come under any presently known clinical entity or etiology. For the purpose of this study we shall refer to this condition as "Lethal Midline Granuloma."

The most vivid and edifying clinical description of the course of this disease is that given by Stewart.[5] He divided the symptomatology and pathological progression of the disease into three stages. He called the first, the prodromal stage; the second, the stage of active disease; and the third, the terminal stage.

The prodromal stage is characterized by intermittent nasal obstruction often accompanied by watery or serosanguinous rhinorrhea. Occasionally, however, the disease may be initiated by the appearance of a superficial ulceration in the nasal vestibule, nasal septum, or soft palate. In some patients, a history of pre-existing infection of the paranasal sinuses can be obtained. Surgical procedures in the nose usually conclude unfortunately. A perforation of the septum and delayed healing may be anticipated following a submucous resection. This stage may exist from several weeks to several years.

In the second "period of active disease," the persistent nasal obstruction becomes aggravated and is accompanied by a more profuse and maladorous purulent or serosanguinous discharge. It is usually of from 10 to 18 months' duration and is the stage when active therapy is imperative before excessive destruction of tissue takes place. The characteristic feature of this stage is the appearance of a gray necrotic patch on the nasal septum, turbinate, floor of the nose or palate. This breaks down rapidly and a shallow ulcer appears. The ulceration spreads progressively from the roof of the mouth or palate to the nasopharynx and nose, and from the inside of the nose erodes outside to the face.

Early in the involvement of the facial tissues, the nose and paranasal structures become indurated and swollen. As the lesion progresses, the palatal, nasal and malar bones, together with the contiguous soft tissues, undergo necrosis and sequestration. Abscesses may develop in the soft tissues, but there is no evidence of severe sepsis. The temperature is irregular,

being normal or slightly elveated, and the leukocyte count may be normal, slightly elevated, or even show a leukopenia.

Agranulocytosis has never been found, and septicemia, as indicated by blood culture, is uniformly absent. The most striking observation of this second phase is that despite the apparent gravity of the destructive lesion, the patient presents an impression of well-being except for varying degress of weakness and lassitude.

In the third, or terminal stage, the prominent features are the obvious exhaustion of the patient and the extreme mutilation of the advancing lesions. The eyelids are swollen and a purulent discharge exudes from between the lids. Numerous areas of swelling and sloughing appear over the lacrimal sac, cheeks and external nose. The destruction may be extreme in some cases, with the loss of the central portion of the face and development of a large central aperture through which the roof of the nose and nasopharynx may be visible. The nasal septum, turbinates and lateral walls of the nose may have been obliterated, leaving the lateral walls of the maxillary sinuses and malar bones exposed. The pharynx and larynx may be extensively necrosed. The margins of the gaping lesion are indurated with rolled, heaped-up tissue covered with a dirty brown or greenish-brown heavy crust, and exuding a fetid odor of putrefaction. Strangely, the tongue remains unaffected and no destruction of the basi-sphenoid has been reported. Generally, there are little or no complaints of pain. At this stage, recurrent hemorrhages, due to erosion through blood vessels, may cause sudden death. Usually, however, the fatality results from exhaustion and inanition with accompanying high terminal temperatures.

DIFFERENTIAL DIAGNOSIS.

Clinically, there is nothing in the gross appearance of these lesions which would differentiate them from specific infectious granulomatous ulcerations or neoplasms in the same locations. The responsibility of the clinician is particularly important in the matter of a careful differential diagnosis and calls for every laboratory aid he can muster.

In observing a number of these cases, it is apparent that the pathologist, as well as the clinician, must be alerted and kept informed of the progression of the lesion. In at least one of our cases, the mere pronouncement of the diagnosis of "lethal midline granuloma" had a tendency to paralyze initiative in searching for active and effective help. It was only through repeated and diligent examination by a number of pathologists that we were able to classify the condition more specifically as of neoplastic character, and thereby institute vigorous countermeasures. The patient is alive today and has been a source of stimulating investigation in this problem (see Case 1).

Diagnosis of lethal midline granuloma is made by history, clinical findings and, most important, by exclusion of other diseases causing similar lesions. Conditions to be considered and excluded in a differential diagnosis can be listed as follows:

1. Syphilis; *2.* Tuberculosis; *3.* Neoplasm; *4.* Fungous infections; *5.* Bacterial or protozoal infections; *6.* Anemia or blood dyscrasias; *7.* Diabetic gangrene; *8.* Erythema multiforme; *9.* Pemphigus; *10.* Wegener's disease; *11.* Leprosy; *12.* Glanders; *13.* Anthrax; *14.* Tularemia; *15.* Yaws; *16.* Leishmaniasis; *17.* Mycosis fungoides; *18.* Noma; *19.* Boeck's sarcoid; *20.* Rhinoscleroma.

Ulceration of the nose instantly suggests syphilis, tuberculosis and neoplasm. It is well to remember that neoplasm may coexist with both tuberculosis and syphilis. X-ray and laboratory studies should include cultures for tubercle bacilli, and negative findings should be confirmed by animal inoculation. Biopsies should be adequate in size and be repeated without hesitation if the diagnosis is in doubt.

Other conditions causing tissue changes characterized by granulomata and local tissue destruction would include fungous infections (particularly actinomycosis, coccidiomycosis and histoplasmosis), Boeck's sarcoid, leprosy, glanders, chronic tularemia, anthrax, rhinoscleroma and yaws.

Biopsies and cultures for the fungi, aerobic and anerobic bacteria, and serological tests for typhoid, tularemia and un-

dulant fever should be done. Biopsies from early lesions are most revealing in histoplasmosis and scleroma.[15]

Forbus[14] stated that etiologic diagnosis of inflammatory granulomatous disease presents very great difficulty in spite of the fact that specific sensitization of the skin is a characteristic feature of some of the granulomatous infectious diseases. Prominent among this group are tuberculosis, brucellosis, tuleremia, typhoid fever, coccidioidomycosis, venereal lymphogranuloma and histoplasmosis. The production of so-called sensitizing antibody may be a feature of granulomatous inflammation, yet a typical granuloma may occur without demonstrable antibodies. It is of interest that other forms of immune bodies may also be present in these infections and are of value in the laboratory tests for differentiation. Complement-fixing antibodies appear in significant quantities in syphilis, coccidioidomycosis and some of the parasitic granulomatous infections. Opsonins, agglutinins, and precipitins appear in brucellosis and typhoid fever. Myiasis and Leishmaniasis, although rare, are the two important parasitic diseases to be considered. Myiasis can be readily ruled out by careful inspection. Naso-oral Leishmaniasis may be difficult to exclude completely because, in the late stages, the Leishmania may be scant or absent.[15] It has been reported that in some tropical areas this parasite can produce early destruction of the nasal septum and necrosis of the alae nasi just as it occurs in syphilis, yaws, leprosy and lethal midline granuloma.[5]

In anemia, agranulocytosis or leukemia, ulcerations about the nose and face can be differentiated from those due to lethal midline granuloma by the blood pictures and natural histories of the diseases. The blood picture in lethal midline granuloma will show the white cells in an approximate normal proportion with no morphological changes.

Pemphigus may manifest itself first in the nose and pharyngeal mucosa in the form of vesicles, necrotic areas and ulcerations. The Macht-Pell phytotoxin test will be of diagnostic aid in suspected cases.[15]

Diabetic gangrene usually attacks the extremities, but may

involve the face. There should be little or no difficulty in determining the disturbed sugar metabolism and its associated vascular changes causing the gangrene.

Gangosa (rhinopharyngitis mutilans) is found in subtropical countries and mostly affects natives. The disease starts as a superficial ulcer on the posterior pharynx or palate characterized by a dirty brown scab. Destruction of the nose and palate may take place.[16] Except for the prognosis, which is rarely fatal, and geographic area from which the patient comes, there is little to differentiate this lesion from the lethal midline granuloma type.[17]

In erythema multiforme, the common papular lesion is characteristic when it forms the "iris" lesion by peripheral extension and central clearing. The histologic appearance is of value.[15]

Another nonspecific granulomatous nasal lesion associated with polyarteritis nodosa, or other collagen disease changes in the arterial system and kidneys, was described by Wegener[18] in 1939. Since then, a number of accounts have appeared in the literature describing granulomata which, while not so locally destructive as the lethal midline type, nevertheless proceed to a fatal issue. Death is usually due to anemia, and postmortem examination reveals changes in the spleen, kidney and other organs suggestive of polyarteritis nodosa.

PATHOGENESIS RELATING TO ALLERGIC TISSUE REACTION.

An important concept in the development of granuloma is the role that the allergic state or local tissue immunity plays in its production. Consideration of the implications of anephylactic inflammation may cast a new light on the basic pathological changes and, therefore, ultimately the treatment of lethal midline granuloma. Most of the recent work in the fundamental nature of granuloma formation and tissue destruction has followed in the path of immunological or stress effects on tissue changes.

An interesting chain of evidence can be collected from the literature relating the pathogenesis of lethal midline granu-

loma to localized allergic tissue reaction. It was shown by Ross[19] that an injection of staphylococcus toxin of varying dilution into immunized rabbits produced either a suppurative or granulomatous inflammation.

Cannon and Pacheco[20] demonstrated that after intradermal injection of living staphylococcus aureus into normal animals, edema of the subcutis with infiltration or polymorphonuclear leukocytes took place. In skin previously immunized, however, there was a heavy infiltration of lymphocytes and monocytes which became massed around a region of bacterial concentration ,and subsequently underwent necrosis with accompanying hemorrhage and thrombosis of the capillaries.

Arthus and Breton[21] demonstrated that if an area of skin is sensitized and antigen is then injected into the area, a pathologic picture similar to that produced in granuloma will result. Gerlach,[79] in addition, described necrosis of the arterioles at the site of the Arthus phenomenon. Arkin[80] demonstrated the similarity in tissue reaction between periarteritis nodosa and granuloma, showing that the former underwent the same necrotic vascular reaction in somewhat larger vessels that caused the Arthus phenomenon when it involved capillaries.

Opie[22] observed that foreign protein injected in immunized animals became fixed at the site of injection, and it was in the immunized area that "anaphylactic" inflammation occurred. This anaphylactic inflammation histologically appeared indistinguishable from that seen in granulomatous inflammation. Finally, Wegener[18] reported a series of cases with pathological studies, where he found periarteritis nodosa to be a common finding in patients with lethal midline granulomatous ulceration. He felt that the condition causing the granulomata and that causing the periarteritis nodosa might be the same.

Kahn[23,24] and his co-workers at the University of Michigan have been engaged in experimental work on laboratory animals, attempting to demonstrate how allergic tissue reactions may lead to the development of lethal midline granuloma. Their work has given us the most direct explanation of the

relationship of tissue changes in immunological reactions, and how it connects with the problem of idiopathic granulomatous ulceration under discussion.

The concept of tissue immunity has been extended and developed by Kahn,[24] who has, in particular, called attention to the defensive properties of the skin and subcutaneous tissue. When an antigenic agent is injected into the skin of an immunized individual, it is anchored locally and is circumscribed by an inflammatory reaction. Kahn[23] found that anchoring of micro-organisms and other antigenic proteins, whether coming from milk, serum, or pollens, is the outstanding defense in the immune state. The widespread prevalence of micro-organisms wherever life exists, and their constant contact with the surface tissues of animals, have produced the localizing mechanisms which aim ultimately not only to prevent invasion of the body, but also to destroy them locally in the area in which they happen to gain entrance. Tissue necrosis in pre-existing inflammatory tissue-antigen reactions was found to be a common immunologic phenomenon by Kahn. He pointed out that it has been seen clinically in infection when the wall which has kept micro-organisms localized in a given focus breaks down, resulting in their escape into the blood stream with a flaring up and necrosis in other pre-existing foci where the cells have become hyperimmunized.

Kahn[24] presented a hypothesis which fits the findings in a lethal granulomatous ulceration in the midline tissues of the face. He stated that through previous infections these naturally reactive tissues might have become hyperimmunized or might still remain nontoxic antigen. Tissue necrosis might then ensue from any specific or nonspecific nontoxic antigen circulating in the blood, possibly even from absorption of "anaphylactogens" through the intestinal wall. Lethal granulomatous ulceration of the nose, pharynx and larynx appears by preference in the midline region because this is a region made up of large areas of skin and subcutaneous tissue in juxtaposition with mucous membrane and submucous tissue. Such tissue has an innate capacity to develop hyperimmunity, possibly greater than any other area in the body. The body tends to respond to invasion by micro-organisms which are

meager producers of toxin principally by two "stereotyped" mechanisms, suppurative and granulomatous inflammation. In the first, the prominent responding cell is the polymorphonuclear leukocyte; in the second, the cells of the reticuloendothelial system, especially the plasma cells and macrophages as local immunity develops.[14] In hyperimmunity states, there is an associated "capillary and lymphatic blockade" with the formation of central necrosis caused by cutting off the blood supply. This is essentially the Arthus phenomenon. Associated with the production of central necrosis is the production of areas of panarteritis in some of the smaller and larger arterioles. This is essentially periarteritis nodosa. It is presumed that the same mechanism working in different sized vessels produces both phenomena. It has been stated that idiopathic granulomatous ulceration and periarteritis nodosa together with rheumatoid arthritis, Lehman-Sacks syndrome, lupus erythematosis and other related conditions, are instances of vascular "allergy."[6]

Menkin[25] found that damaged tissue cells release a substance, necrosin, associated with Gamma globulin, that is capable of producing the central necrosis which Kahn did not explain adequately.

Although the concept of tissue immunity, as outlined by Kahn,[23] is not accepted by all immunologists, its development appears to have been made along logical lines of immunity versus hypersensitivity or allergy. In addition, it has furnished a practical working hypothesis for future research. Boyd,[26] in discussing immunity versus hypersensitivity, recognizes that "almost any kind of body cell can produce some antibody for local concentration." According to Landsteiner,[27] findings which suggest the possibility of local antibody formation in infected sites have been presented by Osterkov and Anderson, Tapley and associates, Sacks, Siegel and associates, as well as Cannon and associates. Williams[6] states that from the viewpoint of phylogeny, Kahn's hypothesis seems highly probable.

Selye[28] presented evidence to indicate that periarteritis nodosa and related collagen diseases would also be produced by exposing an animal to such damaging stimuli as cold,

fatigue, or emotional conflict. This effect was produced by stimulation of the adrenotropic hormone of the anterior pituitary, which in turn stimulated the production of hormones of the adrenal cortex. He found evidence that such stimulation caused a relative adrenal cortical insufficiency. It, therefore, seems reasonable to assume that tissue immunity is a phase of the general adaptation mechanism and that hyperimmunity or bacterial allergy occurs in individuals who have a tendency toward relative adrenal cortical dysfunction. Under this hypothesis, "allergy" would have to be defined in the very broadest of terms.

Wegener[18] concluded that the vascular granulomatous and renal changes were manifestations of tissue hypersensitivity. He suggested that these lesions of lethal midline granuloma should not be separated from lesions found in disseminated lupus erythematosis which may show similar renal lesions, similar arteriolar necrosis and sometimes miliary granuloma.

Klinge,[29] in an experimental pathologic study of these related conditions described the pathological changes as a swelling of the ground substance of the vessels which are involved in the process, with edema, fibrinous degeneration and swelling of the collagen fibrils of the walls of the vessels. Klinge believes nonspecific lethal midline granuloma to be an allergic lesion which pathogenetically is related to rheumatic fever as well as to allergic vascular lesions such as periarteritis nodosa and lupus erythematosis.

Weinberg[30] feels that somewhat similar histologic pictures are seen in oidiomycosis, glanders, tularemia, leprosy, rhinoscleroma, blastomycosis and sporotrichosis, and effort must be made to rule out these organisms as causative agents. He also considered the possibility that a virus might be the causative agent, but stated that of the viruses, only that of venereal lymphogranulomata produces a microscopic picture which is similar. He believes that if these organisms are eliminated insofar as possible, periarteritis nodosa should be considered in the diagnosis. He presents evidence that lethal midline granuloma is an instance of localized hyperimmunity resulting in an Arthus-like reaction of the involved tissue.

PATHOLOGY.

The pathology of the lethal midline granuloma does not have a specific character which would definitely differentiate it as a pathognomonic entity. Pathologists are cautious in reporting sections taken from lethal midline granulomas as being "not typical" or diagnostic of this or that condition, qualifying their impressions by admitting that their diagnoses, which range from granuloma, specific or nonspecific, to neoplasms, are atypical.[31]

The cells of the reticulo-endothelial system undergo successive morphological changes in granulomatous inflammation. These follow in order: proliferation, degeneration, death and dissolution, phagocytosis, mobilization and antibody production. The proliferative reaction is at times so enormous that the lesions often appear as tumors. This is thought to be responsible for the term "granuloma," introduced when the distinction between hyperplasia and neoplasia was not so sharply drawn as it is today. The abundant cells in the proliferative phase eventually disappear unless the inflammatory reaction is ineffective and the patient dies. Thus, necrosis of the reacting cells is characteristic of granulomatous inflammation.[14]

Pathological sections of lethal midline granuloma are generally described as showing broad zones of necrosis. Viable tissue, where present, is noticeably infiltrated by lymphocytes, plasma cells, some neutrophiles and eosinophiles, and with frequent histiocytes. The latter appear to form variable sized accumulations without the appearance of typical tubercles. Histiocytes and fibroblasts marginate zones of necrosis. Occasional mitoses are present, generally in histiocytic cells. As a rule, giant cells of foreign body or Langhans types are rarely evident. Necrosis is of infarct and coagulation types.

Boyd[26] describes the microscopic appearance as "granulomatous in type with epithelioid cells, giant cells and lymphocytes, but the most striking feature is the intense necrosis resembling that of an infarct and possibly due to a marked degree of obliterating arteritis which accompanies the condition. Similar lesions are sometimes found in the viscera as

well as necrotizing arteriolitis and glomerulonephritis, where the cause may be local tissue sensitivity."

Hoover[7] stated that a typical pathological picture would show ". . . the border of the lesion an amorphous mass of necrosis, beneath which there is an infiltration by inflammatory cells, chiefly lymphocytes and macrophages with occasional plasma cells. A few polymorphonuclear leukocytes are also present. The large vessels show a definite perivascular cuff of lymphocytes and macrophages with degeneration of the arterial wall in some cases."

McCart[32] found that after the initial proliferation of fibroblasts, "the polymorph aggregates disappeared and with the development of collagen, the (lethal midline granuloma) lesion resembled nonspecific granulation tissue, but behaved very differently because it was invasive. When the granulation tissue reached a medium sized arteriole, it infiltrated all coats without destroying them. When the granulation tissue had matured and become fibrous, a greatly thickened arterial wall resulted."

It is evident that various pathologists, in presenting pathological descriptions of lethal midline granuloma, follow essentially the general picture of nonspecific inflammatory granulation tissue, showing no pathognomonic features. Because of this lack of recognizable characteristics many lesions are grouped under this term which further study would yield more definite diagnoses.

Prodda and Guenzi[34] reviewed the histological picture of several reported lethal midline granuloma cases, particularly in the German, French and Italian literature, and felt able to establish the diagnosis of malignant tumor of the reticuloendothelial system in these cases. They state that the histological structures resemble various forms of sarcoma or one of the lymphomas. Some of the neoplastic diseases suggested are Hodgkin's sarcoma, reticulum cell sarcoma, mycosis fungoides, lymphoepithelioma, and Kaposi's sarcoma. DeFaria and his co-workers[35] reported three cases previously considered lethal midline granuloma which they were able to establish as reticulosarcomata. The neoplastic tissue may present

a "polymorphic structure with inflammatory-like cells such as lymphocytic, monocytic and plasma cells conspicuous in the tumor." They state that the matrix cell is the "undifferentiated mesenchymal cell (Maximow[36]), or the dedifferentiated macrophagic cell" which they found through vital staining. (Our American pathologists would probably call this a reticulum cell.) They quoted other reported cases of lethal midline granuloma which were subsequently shown to be malignant processes (Piquet,[37,38] Terracal,[39] Pirodda and Guenzi[34]). Piquet thinks that these tumors may originate as a reticulosis of the histiomonocytic type, but there are also mixed epithelial and gangrenous forms.

The improvement or cure of lethal midline granulomas with radiation therapy in cancercidal doses would support the neoplastic origin of many of the lesions reported. Terracal[39] collected eight cases from the literature, of which six were cured and two improved. Good results following cancercidal radiotherapy were also pointed out by Vilanova,[40] Causse,[41] Ellis[42] in two cases, Howell,[43] and Alajmo.[44]

TUMORS MASKING AS LETHAL MIDLINE GRANULOMAS.

The ulcerative necrotic lesion appearing as so-called lethal midline granuloma may effectively mask a neoplastic process, as has been shown above (Pirodda and Guenzi,[34] DeFaria,[35] Terracal[39]). This is not strange, because lymphoepithelial tumors in this location grow so quickly beyond their available blood supply that necrosis and ulceration takes place readily.[46] Because of their location in the nose and throat, secondary infection is inevitable. These factors combine to produce a necrotic base with a large inflammatory component in which only small residues or fragments of tumor can be found. The result is that these small aggregates of neoplastic tissue, obscured by areas of necrosis and inflammatory cell infiltration, are easily missed or misinterpreted in random biopsies. This is illustrated in Case 1 of our series, in which the biopsy was reported as nonspecific inflammatory granulation tissue. Subsequent biopsies, after the superimposed inflammatory infiltration subsided following Cortisone therapy, established the lesion as of neoplastic origin.

Such ulcerating carcinomas, leaving only small traces of intact tumor, are well known in the skin, where they have been mistaken for syphilis or other chronic granulomas; in the stomach, where they are mistaken for benign peptic ulcers.[47]

In studying and reviewing the various neoplasms which may be masked by the lethal midline granuloma of the nose and face, the most likely types would include lymphoepithelioma, Hodgkin's disease, mycosis fungoides, and reticulosarcoma. All but lymphoepithelioma of the nasopharynx offer valid objections in answering all requirements and fitting the clinical picture most consistently.

Lymphoepithelioma[48] is the chief characteristic tumor of the nasopharynx in the younger and middle age group. The histologic structure,[49] with its component of lymphocytes, easily lends itself to interpretation as an inflammatory granulatomous lesion when there are only small, distorted and partially necrotic remnants. It is composed of a network of undifferentiated squamous cells, and in the meshes of this network are lymphocytes. The two elements are always intimately related. The neoplasm is generally of rapid growing nature and such tumors, as has been stated, tend to necrotize readily. These tumors are also radiolabile so that moderate amounts of radiation therapy may suppress the neoplasm temporarily with accentuation of the necrosis and inflammatory base.

One is impressed, therefore, with the fact that lymphoepithelioma of the nasopharynx, with its charatceristic location, consistent age grouping, and histologic structure, most closely resembles the necrotic ulceration seen in the lethal midline granuloma of the nose and face. The tumor is found in structures which are anatomically and embryologically related.[36,50] Beyond the nasal and pharyngeal regions, it is found also in the tonsil, other portions of the hypopharynx, and base of the tongue, *i.e.*, where lymphoepithelioma tissue normally exists. It is also the chief characteristic tumor of the thymus, another lymphoepithelial organ. According to Arey,[50] the histogenesis of these structures from the second, third and fourth gill clefts relates them.

It would seem logical, then, that the lymphoepithelial structures, and the tumors derived from them, deserve to be regarded separately as an entity, and to be differentiated from the lymphomas on the one hand (Gottfriedson[52]), and from the non-keratinizing squamous cell carcinomas (formerly called "transitional cell carcinomas") on the other (Ewing,[53] Quick and Cutler,[54] Willis[51]). The European writers have long made this distinction; in the Orient, the tumor is well known because it is rather common (Mekis[55]); and the concept has gradually been adopted in England and the United States. Trotter,[56] in 1911, described clearly the characteristics of this tumor, and in 1921 Schminke and Regaud[48] aptly named it lymphoepithelioma, a term which has remained in use. Capell,[57] Harvey[58] et al., Willis[51] and others have described its essential features.

The great variety of opinions, ranging from granulomatous inflammation of an unusual type to atypical neoplastic disease, illustrates the lack of pathological conformity and points to the heterogenous character which the term lethal midline granuloma embodies. Increasing awareness of specific causes, and reluctance in accepting the diagnosis of lethal midline granuloma except as a convenient tentative working diagnosis, will decrease the number of cases acceptable as idiopathic. Thus, in reviewing older reports, such destructive facial granulomas considered idiopathic at the time of their publication, seem to be attributable, in the light of present knowledge, to more specific causes. Fordyce[75] reported a "case of undetermined tropical ulcer" in a native of Central America which strongly suggests the possibility of American Leishmaniasis.[69] A case of Henry Macnaughton Jones[74] was considered by the discussants as factitial, and the author had, himself, entertained that possibility. Similarly, Naborro's report of an 11-year-old girl whose condition was cured in 14 days by the oral administration of extract of the common alder may have been factitial. Occasionally, other rare occurrences may lead to somewhat similar clinical pictures, as in the case of a foreign body granuloma of the nose due to gauze left following an injury (Pearlman[78]).

It is, of course, quite likely that in future years when case

reports and diagnoses of our time are reviewed, similar re-evaluations will be made and more specific diseases will be recognized. It is quite probable that lethal midline granuloma will then, with scientific certainty, be laid finally to rest.

CASE REPORTS.

Case 1. A white man, 33 years of age, was first seen in consultation Sept. 17, 1951, because of stuffiness in the left side of the nose and sore

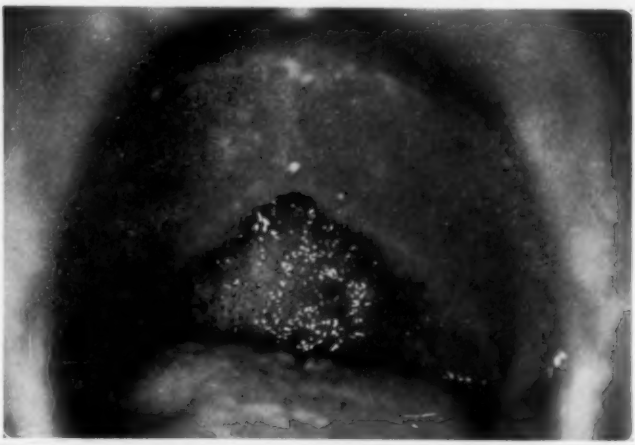

Fig. 1. (Case 1).—Progression of destruction of palate and posterior pharyngeal wall.

throat of about six months' duration. He had lost about ten pounds in weight in the preceding two months and felt increasing fatigue at work. The past history revealed that he had a tonsillectomy three years previously, and while in the Army six years before, he had been hospitalized for an involvement of the nose and throat. The personal and familial histories were not contributory.

Examination revealed a thin, afebrile, normal appearing male, in no distress other than that incident to the nose. A firm granulation was seen on the left inferior turbinate obstructing the nose, and moderate edema of the soft palate was noted. The posterior pharynx behind the soft palate was red, moderately swollen and covered with a thick, gray, purulent crust; there was no adenopathy.

The blood count showed no anemia and a relatively normal distribution of white cells. The Kolmer and Kline tests were negative for syphilis. Smears and cultures of the purulent exudate in the throat and nose were reported to contain staphylococcus aureus, pneumococcus and streptococcus hemolyticus, but were negative for acid-fast bacilli.

Guinea pig inoculation subsequently failed to show acid-fast bacilli. Skin tests for coccidioidin and histoplasma were negative. A biopsy specimen from the left nasal turbinate was reported as "chronic granulomatous rhinitis." The pathologist noted, ". . . chronic inflammatory reaction in a tissue which is covered by a slough. Although occasional foamy cells are seen in the chronic inflammatory reaction, the general pattern does not fit that ordinarily seen in scleroma. There is no suggestion of neoplasm in this tissue." X-ray report indicated hyperplastic sinusitis without bony involvement. The chest film showed normal findings.

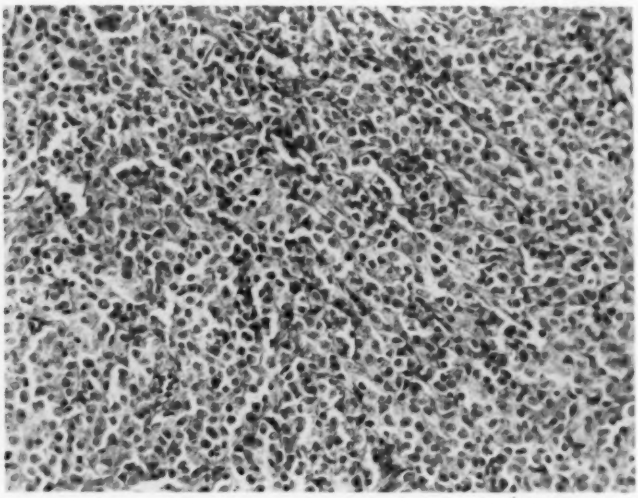

Fig. 2. Section of nasal lesion after subsidence of inflammatory exudate showing principal cell larger and more epitheliomatous in appearance with mitotic figures.

The patient was given penicillin intramuscularly and sulfadiazine orally, as well as bacitracin ointment locally. The condition did not show any improvement. A week later, a gray necrotic area appeared on the soft palate and spread rapidly until the central portion of the soft palate, excluding the uvula, was involved. An ulcerated, sloughing area developed in the center of the necrotic path. Another biopsy was done to include the ulcerate border of the lesion. This was reported as ". . . deep invagination surrounded by epitheliomatous outcroppings which, because of its arrangement and appearance, is considered to be a pseudo-epitheliomatous hyperplasia." The pathologist noted a chronic inflammatory cell infiltration with a granulomatous blood vessel pattern.

The patient was continued on penicillin, 600,000 units daily; streptomycin in 0.5 Gm. doses was added; and terramycin was substituted for the sulfadiazine. The destructive ulceration progressed until about half of the soft palate was destroyed. A gray sloughing ulcer was present

on the pharynx, and a similar necrotic slough was noted over the left inferior turbinate of the nose.

On Oct. 25, 1951, Cortisone was begun with 300 mg. daily and was gradually decreased to a maintenance level of 100 mg. daily. Improvement was noted the next day and continued until the gray slough disappeared and the ulcerated borders began to show healing. The patient's general health improved and his mental attitude indicated more optimism.

A biopsy specimen taken Nov. 6, 1951, was reported that with subsidence of the inflammatory cells, the principal cell involved had a more epitheliomatous appearance and frequently exhibited large nuclei and occasional mitotic figures. Consultative opinion now favored a diagnosis of lymphoepithelioma. The tissue was extensively necrotic, and abundant lymphocytes obscured the epithelial framework, making diagnosis difficult.

After improvement lasting almost three months, the palatal and nasal ulceration and necrosis again became evident. The process became rapidly destructive and another biopsy was performed. A diagnosis of atypical lymphoepithelioma was made and was confirmed by still another biopsy, as lymphoepithelioma.

In view of the deteriorating condition and massive destruction, cancercidal radiation therapy was started through an intra-oral cone measuring 3.5 cm. in diameter, a right and left lateral nasopharyngeal port measuring 10 cm. in diameter, and a right and left antral port measuring 5 cm. in diameter. Over a period of approximately 33 treatment days, dating from Jan. 25, 1952, to Feb. 18, 1952, the patient received an estimated tumor dose of 4855 Roentgen units measured to the midline of the palate. Progress biopsy reports showed tumor cells undergoing excellent radiation effects and encouraged radiation therapy to the limits of tolerance. He was given an additional 1000 Roentgen units measured in air delivered through each antrum, directed toward the midline, until Feb. 29, 1952. There was an initial increase in the swelling and destruction, but this disappeared after a few days. After this his reaction to the radiation therapy was uneventful, and on April 11, 1952, the reaction had completely subsided; no visible evidence of residual disease was noted, although the defect in the palate persisted.

The palatal lesion showed slow but progressive healing until the gray crusting and ulcerated edges became smooth and free of exudate. He has been observed regularly since and has resumed his work. His last visit to our office for observation, on Nov. 8, 1956, more than five years since the onset of the lesion, showed the patient to be in good health with no evidence of recurrence.

Comment. This case illustrates how the underlying neoplastic process was masked by necrosis and chronic inflammatory cells. Cortisone was given to this patient when its administration was new and its effects still uncertain. When the diagnosis of neoplasm became apparent with succeeding biopsies, it was thought that the Cortisone may have caused the metaplasia from chronic granulation tissue. We consulted various sources, and Dr. Henry Williams expressed the opinion that we might be dealing with a Krompecker epithelioma. He stated that at the Mayo Clinic, great difficulty was encountered at times in differentiating this type of tumor from a

midline granuloma. He recounted a similar recent experience dealing with one of these destructive epitheliomas: "The pathologists were able to decide that it was a malignancy only after a great delay and very careful study, because of the tremendous amount of infection present in the tumor." He concluded correctly, as events subsequently proved, that "the Cortisone had the effect of abolishing the inflammatory reaction and allowed the malignant nature of the lesion to become more evident."

Case 2. This 27-year-old white woman was first seen at the Los Angeles County Hospital on Dec. 8, 1949. She complained of persistent sore throat

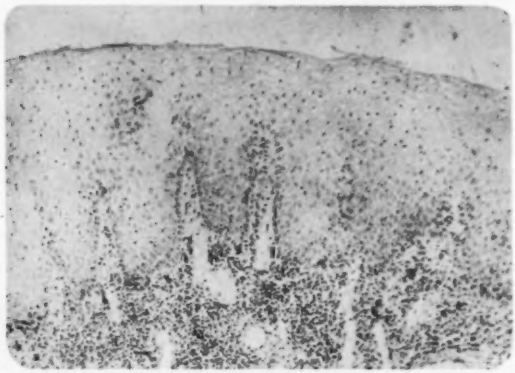

Fig. 3. (Case 2).—Section obtained from nose showing chronic inflammatory infiltration (X125).

of six weeks' duration. She had been treated by her family physician with throat irrigations and penicillin but had shown no improvement. Her past history revealed that she had had epileptiform seizures since childhood. The familial and personal histories were not pertinent. There was no contact with tuberculosis or coccidioidomycosis.

Physical examination on entry disclosed the patient to be a well developed, thin, white woman who appeared in good general health and was afebrile. The relevant findings consisted of a small granulomatous lesion with a 1-cm. perforation on the soft palate near the base of the uvula. There was a midline area of erosion of the hard palate, covered by a tenacious gray exudate. The left side of the nose was obstructed by a red, swollen area along the floor and septum which bled easily on slight trauma.

Laboratory studies showed a blood hemoglobin concentration of 11.8 Gm. per 100 cc., 4,600,000 erythrocytes and 6,500 leucocytes per cubic millimeter with a normal differential count ratio. The serologic test for

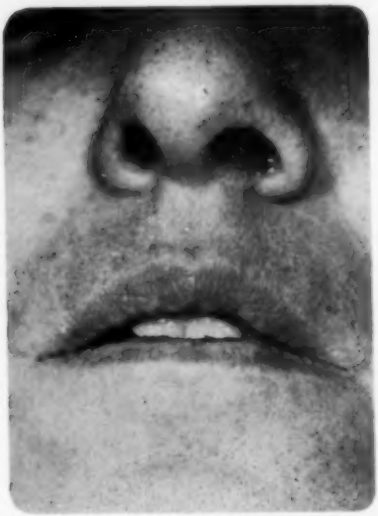

Fig. 4. Case 2).—View of mass on left side of nose at base of septum.

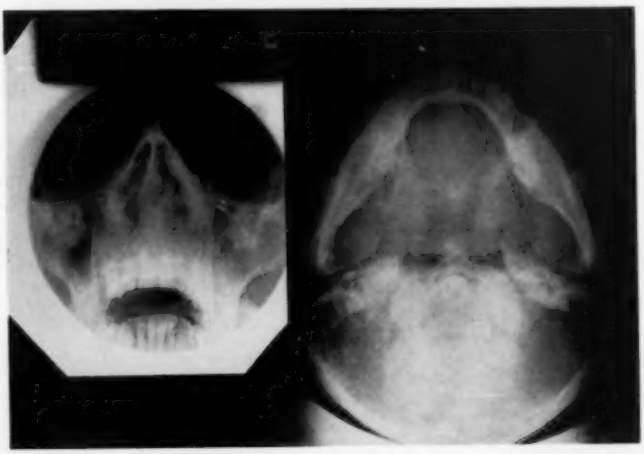

Fig. 5. (Case 2).—Roentgenogram showing opacity involving left half of the nasal cavity and the base of the septum causing deviation and obstruction.

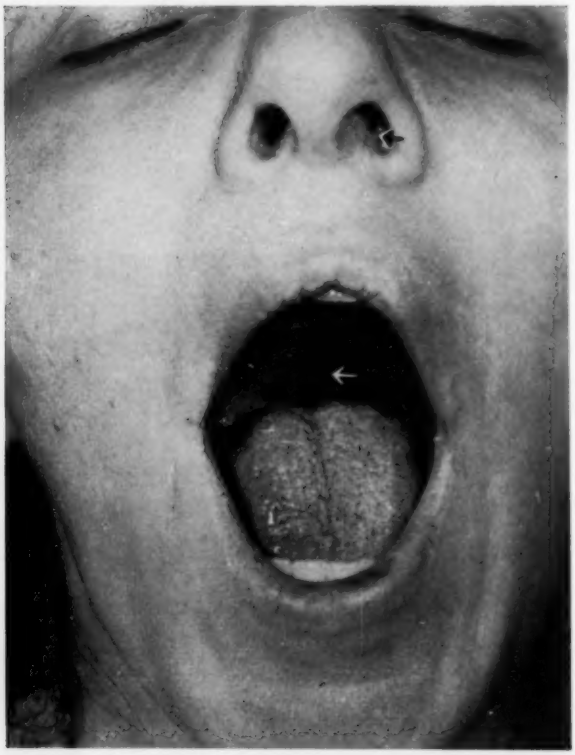

Fig. 6. (Case 2).—Granulomatous mass on nasal septum and ulcerating granuloma on palate, six months after onset of illness.

syphilis, the complement fixation tests for coccidioidomycosis, and the serum agglutination test for typhoid, paratyphoid, brucellosis, tularemia and cold agglutinins, all showed negative results. No sugar or albumin was present in the urine. Examination of the cerebrospinal fluid disclosed no abnormal findings. Tuberculin, coccidioidin, histoplasmin and Frei skin tests gave negative results. No acid-fast bacilli were found on nasal, palatal and sputum smears, and cultures of the palatal lesion showed candida albicans on two occasions, but no other fungi were ever found. Repeated aerobic and anaerobic cultures revealed streptococcus viridans and staphylococcus albus.

She was given penicillin, 300,000 units intramuscularly daily for prolonged periods up to a total of 25,000,000 units; streptomycin, 2 Gm. daily, later reduced to 1 Gm. daily intramuscularly for about three weeks; aureomycin 1000 mg. orally every day for one month; saturated solution

of potassium iodide orally, 30 to 90 minims daily in divided doses for two weeks (because of findings of candida) and antimony in the form of Fuadin, 5 cc. intramuscularly, three times weekly for three weeks (because of similarity to anaerobic streptococci lesions).

There was no response to any of the medication. The soft and hard palates became ulcerated, necrotic and finally a perforation resulted. A biopsy specimen taken from the soft palate on Jan. 6, 1950, was diagnosed as "granulation tissue—nonspecific." A splenic smear examined for histoplasma capsulatum showed no organisms. Complement fixation tests and cultures for rhinoscleroma gave negative results. X-ray examination of the nasal bones and sinuses showed an opacity involving the left half of the nasal cavity, with the septum and tip of the left nasal bone deviated to the right. On a lateral view of the nasopharynx, a circular tumefaction was noted just anterior to C_1 and another tumefaction bulging in the epipharynx and posterior choanal region.

Another biopsy specimen was obtained March 3, 1950, resulting in a diagnosis of "granulation tissue with overlying mucous membrane—probably an infectious granuloma." In the middle of June, the destruction of the palate extended into the posterior choana, nasopharynx and septal region. The turbinates were swollen and bled easily. The fever became of septic type reaching 104° at times. Convulsions, diagnosed as of the Jacksonian type, became more frequent and occurred as often as several times a day. The patient had lost about 60 pounds during the preceding six months. The course was progressively downhill, and she became mentally cloudy during the last three days of life. The patient expired approximately 10 months after the onset of her throat symptoms.

Postmortem examination of the nasopharynx, soft palate and nose revealed most sections to be necrotic, but one section showed a tumor composed of small cells near the size of monocytes supported by a delicate fibrous reticulum. There were many mitotic figures. Other areas of the same mass showed characteristics of transitional cell tumors. It was the opinion of the examining pathologist that this was definitely a tumor with secondary infection, rather than a granuloma.

Comment. This case illustrates pointedly the need for deep and thorough biopsies. The secondary infection and necrosis thoroughly masked the underlying neoplasm. It is possible that if Cortisone had been available at the time, the inflammatory reaction may have subsided enough to facilitate recognition of the neoplasm.

Case 3. A 34-year-old colored male with a history of a "painful sore" on the roof of the mouth of two weeks' duration, was seen at the Los Angeles County Hospital, Jan. 28, 1954. He stated that he may have scratched the roof of the mouth with his finger. He felt "feverish" and experienced chills and fever at the onset. The pain was dull aching in character and was associated with a feeling of fullness and aching in the neck. The chills and fever recurred every night, and the mouth pain became progressively worse. He gave a past history of alcoholism of about 10 years' duration. Two years prior to his present hospital entry, he had a bout of gastro-intestinal symptoms characterized by a steady gnawing pain over the epigastrium, which was relieved by food. In addition, in the past three years he had a productive cough which he attributed to smoking. He had a negative minifilm examination of his chest taken by a mobile unit three years previously. A luetic infection was present when he entered the Army in 1944. He was given a six-

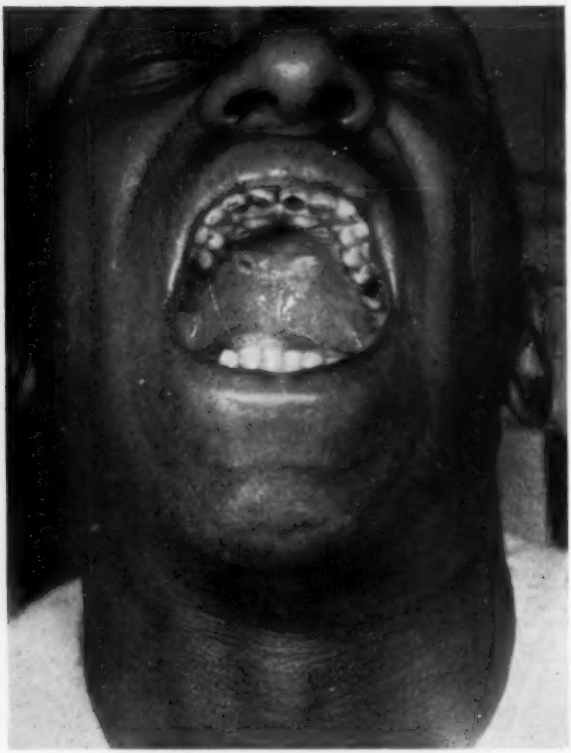

Fig. 7. (Case 3).—Photograph of palate showing ulceration and necrosis three weeks after onset.

month course of treatment and told that he was cured. Subsequent blood tests proved negative for syphilis.

Examination revealed a well nourished Negro male with a temperature of 99° F. in no distress. An irregular white, necrotic area measuring about 4x4 cm. was seen over the hard palate extending through the mucous membrane, and further extending by perforation into the nasal cavity. A few movable shotty nodes were present bilaterally in the neck. Several carious teeth were noted in the mouth, and an old scar over the cheek. The other physical findings did not reveal any abnormalities.

X-ray of the chest and face showed no bony abnormalities except for a defect in the hard palate. X-ray examination of the gastrointestinal tract showed a shallow ulcer on the lesser curvature of the stomach. A complete blood count showed a normal number of erythrocytes and white

blood cells with a normal cell distribution. Stain and culture of his sputum showed no acid-fast organisms. Urinalysis was negative for albumin or sugar. Smear and culture of the lesion showed Gram positive cocci and Gram negative bacilli, but no acid-fast or diphtheria bacilli. The heterophile antibody agglutination was negative. No fungi were grown in culture, and skin tests for coccidiomycosis were negative. Blood sugar determination did not indicate evidence of diabetes. The Kolmer and Kahn tests were both negative, and a spinal fluid examination also resulted in a negative serological reaction for syphilis. A biopsy specimen of the lesion showed "nonspecific chronic granulation tissue without evidence of malignancy." The pathologist believed the lesion to be consistent with a "diagnosis of a so-called midline granuloma."

The patient was given tetracycline, 2000 mg. daily for five days without demonstrable improvement. He was then placed on 1,200,000 units of penicillin and streptomycin 1 Gm. daily. At the end of two weeks, the lesion continued to show progressive destruction and a slough fragment of necrotic ulceration was again examined for micropathological diagnosis, smear, and culture. The microscopic examination showed "nonspecific and necrotic granulation tissue." Smear and culture showed a mixed staphylococcus and streptococcus flora.

In spite of the gastric ulcer, and in view of the grave prognosis of a lethal midline granuloma, the patient was placed on 50 mg. of ACTH intramuscularly daily. He was given potassium chloride 45 grams daily and placed on a low salt diet. No activation of the ulcer took place, and the amount of ACTH was increased daily, first to 120 mg. intramuscularly and finally, after he had been on intramuscular administration for 10 days, he was given 120 mg. ACTH intravenously in 1000 cc. of 5 per cent glucose continuously over a 24-hour period for four days. Uropepsin content of the urine was checked before and after the intravenous infusions to check activation of the gastric ulcer. Intramuscular injections of ACTH in 120 mg. daily doses were then resumed. The patient began to show improvement within the first week after ACTH was administered but demonstrated more rapid healing coincident with the intravenous administration. Epithelialization became evident, and the defect began to fill in slowly over the next three-week period. His general condition was greatly improved, and he was transferred to the Veterans Hospital, where he continued to take the ACTH.

Our last reports from the Veterans Faculty were that the palate defect finally filled in and he was discharged six weeks later feeling well. An attempt was made to contact him this year, but his present forwarding address is unknown.

Comment. The lesion in this patient showed no response to antibiotics, but improved dramatically with the corticotropins. This would indicate that the lesion is probably of the group associated with "allergic" tissue changes related to the collagen disease although no vascular changes were seen in the biopsy specimens. It is also of interest that the gastric ulcer found in this patient would also be associated with stress, and may show some relationship in response to the cortico-steroids.

Case 4. A white male, 42, was first seen in February, 1951, with a presenting complaint of swelling and discomfort of the right lower jaw bicuspid region. He stated that this followed the use of a penicillin troche

a week previously, after which the swelling "spread like wildfire." The remainder of the right lower jaw was involved and pain became severe and widespread over the face. He gave a past history of duodenal ulcer at the age of 36, with hemorrhage. He had undulant fever at the age of 31. Otherwise the patient had always been in good health and was athletically inclined until about five months prior to the present onset, when he felt weak and listless.

He was first admitted to St. Vincent's Hospital on March 19, 1951, because of swelling of both upper and lower gums and hemorrhagic eruption over the alveolar mucosa. The red blood count was 5,400,000, and the white blood count 5,500 per cubic millimeter with a normal cell distribution. The platelets appeared normal in number and morphology.

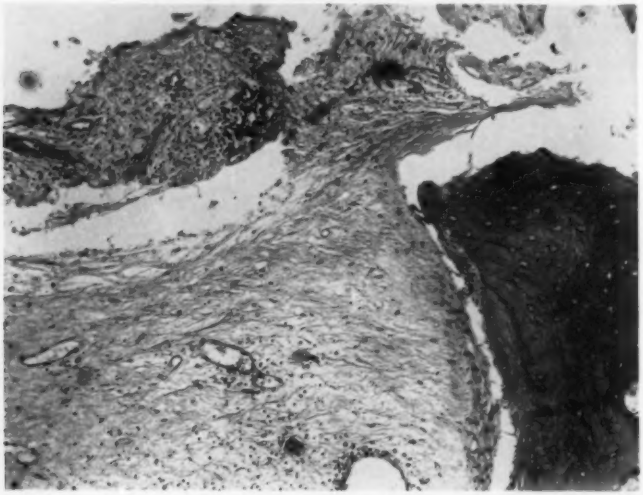

Fig. 8. (Case 4).—Section of mastoid obtained at autopsy (X125) showing scattered micro-abscesses surrounded by fibroblasts and a dense exudate of plasma cells, lymphocytes and large number of macrophages.

The blood culture was negative after 48 hours, and the agglutinations for Brucella were negative in all dilutions. Biopsy of the gum tissues showed a suppurative inflammatory process without definite bacteriological diagnosis. He was given aureomycin, 1000 mg. daily and streptomycin, 1 Gm. intramuscularly daily. The febrile reaction and pain subsided but did not entirely disappear. He was discharged from the hospital and continued under observation in the office.

The condition grew steadily worse, and he was readmitted to the hospital on April 18, 1951. The oral surgeon in attendance noted at this time that the gums were dark red and swollen. Miliary abscesses were distributed over the surface. The patient noted pain in the ears with increasing deafness on both sides. The otological consultant found no gross changes in the ears. The deafness was of the mixed type and

ranged from 32 per cent on the right to 42 per cent on the left in air conduction; 25 per cent on the right and 40 per cent on the left by bone conduction. Biopsy at this time showed multiple punctate abscesses with chronic round cell infiltration and fibroblasts in the submucosa. There was no primary vasculitis or specific pathognomonic pattern. He was maintained on tetracycline antibiotics with only slight regression of the lesions.

On June 4, 1951, he was placed under the care of an internist and admitted to the hospital for a complete and comprehensive examination. At this time, it was noted that along with the gum lesions he had generalized skin sensitivity, and a weakness of the left side of the face became evident. The patient felt weak and had an irregular fever ranging from 100° to 106° F. A diagnosis of possible Reiter's syndrome was made. It was felt that one of the collagen diseases (particularly periarteritis nodosa), lymphomas and leprosy should be ruled out. Nasal scrapings were examined for leprosy and repeated smears and cultures did not yield any spcific incriminating organisms. Both ears were found to be draining a mucopurulent secretion. It was the otologist's opinion that this was due to the systemic process causing swelling throughout the upper air passages and including the Eustachian tubes. An X-ray of the sinuses showed minimal haziness in the sphenoids and right antrum.

The antibiotics were stopped and he was placed on ACTH therapy. This resulted in improvement of the mouth lesions, and he was discharged from the hospital. He continued on ACTH, while at home, receiving injections of 80 mg. daily. After three weeks it was found that the response to ACTH was fair, but dosages under 100 mg. daily resulted in exacerbation.

He was readmitted to the hospital for neurological examination, including a spinal tap, because of increasing headache and pain over the face. The neurologist confirmed the findings involving the VIIIth nerve deafness and VIIth nerve facial palsy, which he felt were peripheral in type and due to compression. He came to the conclusion that the condition fit most consistently as a part of collagen disease involvement rather than a specific neurological lesion.

An epidemiologist in consultation felt that there was no Hansen's disease or Steven Johnson syndrome. Hematological consultation and bone marrow study revealed reactive marrow without evidence of neoplasm. There was a remission in his symptoms of pain and he was discharged home.

On Aug. 7, 1951, the patient experienced severe epigastric pain, nausea and vomiting, and was readmitted to the hospital. The facial palsy persisted and the headaches continued in increasing severity. In the course of his examination the blood chemistry determination, blood count and clotting time all proved to be within normal limits. A peritoneoscopy was performed and showed no conclusive results. The abdominal symptoms subsided, but the pain over the face and head increased. There was tinnitus and a "dizzy swirling sensation." It was obvious that the patient's condition was steadily growing worse. An exploratory craniotomy was performed on Oct. 19, 1951, and the left cerebellopontine angle was explored. No space occupying lesion was seen, but granulation tissue was noted in the region of the VIIth and VIIIth nerves. Some of the granulations were removed for histological diagnosis. The patient did not rally, becoming increasingly comatose, and finally expired with a terminal fever of 106° on Oct. 22, 1951.

Postmortem examination showed granulomatous tissue distributed in the nose, paranasal sinuses, ears, meninges, kidneys and prostate. In the brain the granulomatous process was limited to the dura and small

patches of pia arachnoid, but nowhere did the process occur within the parenchyma of the brain. It was remarkable that all the cranial nerve were entirely uninvolved by this granulomatous process. Even the Ist and IInd nerves passed through the involved dura without the exudate appearing to more than compress them, certainly not to infiltrate them.

The microscopic appearance of the granulomatous infiltration was found similar in all the involved organs. The process had the characteristics of a granuloma. There were scattered micro-abscesses consisting of partially necrotic neutrophiles. These formed irregular pockets. The micro-abscesses were surrounded by fibroblasts, in which were found occasional epithelioid-like cells but with little leukocyte exudate. Beyond the fibrous tissue surrounding the micro-abscesses there was a dense exudate of fibroblasts, lymphocytes, plasma cells, large numbers of macrophages and occasional neutrophiles, and only very rare eosinophiles. The pathologist felt that "the granulomata look as though they should be caused by some type of fungus, but no etiological agent can be demonstrated." Only in the dura were there a few foreign body type giant cells found within the exudate, but nowhere was there any typical tubercle formation. No vascular lesions could be seen.

The bizarre clinical course and findings in this case proved to be due to a generalized, parenchymal granulomatous process. Neither during life nor after death was a specific etiologic agent found. This disease, therefore, is believed to fall into the group of ulcerative granulomata related to Wegener's syndrome, which is a so-called collagen disease. It appears consistent with this category, both clinically and histologically, except that in this case there was no evidence of vasculitis of any sort.

Case 5. A Negro male, age 72, reported to the Otolaryngological Clinic of the Los Angeles County Hospital on July 19, 1950, with complaints of increasing sore throat and pain upon swallowing of two years' duration. His past, familial and personal histories were non-contributory.

The physical examination showed an extensive ulceration of the soft palate with destruction of the posterior third. A large, firm, gray-pink mass was seen in the nasopharynx extending into the oropharynx. The nose was obstructed on both sides by heaped-up masses involving the floor and the septum. A large perforation was present in the septum with the edges of the perforation ulcerated and swollen. He was afebrile and showed no distress other than that related to his throat.

The blood count showed a moderate leukopenia. The Wasserman and Kolmer tests were negative. X-rays of the sinuses, skull and chest did not show any destructive process or metastasis. Biopsy specimens obtained from the palate and nose were described as "inflammatory exudate with necrosis adjacent to a fibrotic area, which is submucosal; there was no evidence of specificity. The findings are not remarkable except for associated inflammatory changes." Smear and culture of the nose and palate lesions showed staphyloccoccus albus, streptococcus and candida albicans. There was no evidence of rhinoscleroma or diphtheria. Skin tests for coccidioidin showed an area of 2 cm. erythema and 1.5 cm. induration on the forearm. Skin test for histoplasmin was negative.

The patient was hospitalized and placed successively on penicillin, achromycin and streptomycin without his making any improvement. A

second biopsy of the palate and nose was diagnosed as "nonspecific granulation tissue and necrosis without evidence of malignancy. The findings are consistent with a midline granuloma."

The ulcerative process continued to destroy the palate, causing the loss of the entire soft palate and about a third of the hard palate. The floor of the nose, remaining septum, the nasopharynx and the palate appeared to be invaded by an indurative, firm, gray-pink, irregular tumor, which almost filled the nasopharynx and posterior nares. An extensive and deep biopsy specimen from the palate, nose and nasopharynx was examined by several pathologists. The micropathological diagnosis of the lesion was given as "typical of Ackermann's verrucous carcinoma." This was described as a non-metastasizing, locally invasive malignancy. The intensive antibiotic therapy helped to clear the secondary infection and relieved the throat soreness and painful swallowing, but it did not affect the destructive course of the lesion.

He was observed in the clinic without his showing any improvement. X-ray therapy was given in weekly doses from May 28, 1951, to Oct. 12, 1951. At the end of the course of X-ray treatments it was felt that the lesion had regressed partially, and the patient was asymptomatic. In the course of the next month, the destructive process appeared active again with increasing soreness of the throat and painful swallowing.

He was again admitted to the hospital and was placed on ACTH therapy; however, this had to be stopped after four days' administration because of marked increase in blood pressure to 270/140 and left congestive heart failure. The administration of digitalis, low salt diet and ammonium chloride gradually helped, and he was discharged home. A biopsy at this time was diagnosed as "pseudoepitheliomatous hyperplasia with evidence of Ackermann's verrucous carcinoma."

In the following four months, the patient showed progression of the lesion and had numerous admissions to the hospital. During one admission he was placed on bismuth subsalicylate and potassium iodide as a therapeutic test for lues, but he did not show any improvement. The lesion progressed until it involved the whole nasopharynx, hard palate and posterior half of the nose. He had frequent episodes of nasal bleeding, developed ankle edema and orthopnea. He died of a terminal bronchopneumonia.

An autopsy could not be obtained.

Comment. In this case, the diagnosis of lethal midline granuloma was established on the basis of preliminary biopsies which showed nonspecific granulation tissue. Aided by the intensive antibiotic therapy which cleared the secondary infection, it was possible, with subsequent extensive and deep biopsies, to establish the diagnosis of an atypical neoplastic lesion. Unfortunately, this type of tumor was not susceptible to X-ray therapy and not amenable to surgery.

Case 6. This 62-year-old Negro man presented himself to the Otolaryngological Clinic of the Los Angeles County Hospital on March 30, 1949. He gave a history of increasing difficulty in breathing through the nose for the past three months. His past history included a hospital admission in 1937 for pulmonary tuberculosis. At that time note was also made of hypertension and early cardiac enlargement. He was under observation by the Health Department and was discharged as an arrested and

inactive case of tuberculosis. There were no further manifestations of acid-fast infection.

Examination revealed a thin, afebrile Negro male in no distress. A large fungating mass was seen originating on the floor of the nose at the anterior portion of the septum. This mass extended from the anterior septal area to the posterior choana on both sides. It was friable and bled easily. His other general findings indicated a moderate hypertension and enlarged heart without evidence of decompensation.

Serological tests for syphilis were negative. X-ray of the chest, although showing extensive scarring from the old infection, did not show any presently active process. Sputum studies and culture showed no acid-

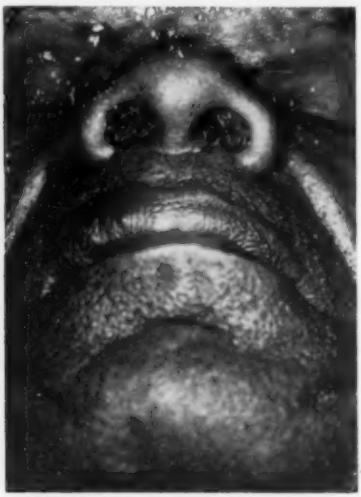

Fig. 9. (Case 6).—Masses in both sides of nose involving the floor and septum.

fast organisms. Biopsy specimen of the mass in the nose was reported as "infected granulation tissue showing no specific features. Midline granuloma should be considered." Another biopsy was interpreted as "chronic inflammation with pseudoepitheliomatous hyperplasia."

Because of his past history of tuberculosis, the patient was placed on streptomycin and given a total of 14 grams, divided in 1 gram daily doses, administered intramuscularly. No improvement was shown, and another specimen was submitted for examination. The micropathological diagnosis was reported as "chronic granuloma with epithelioid tubercle formation compatible with either tuberculosis or leprosy, but acid-fast stain showed no organisms." Material was curetted from the lesion for culture. No growth resulted. The smear revealed staphylococcus aureus, coagulase positive. The coccidioidomycin complement fixation test was negative, and aerobic and anaerobic culture for fungi did not show

growth. Repeated subsequent biopsies showed chronic granulomatous inflammatory tissue with small tubercles and giant cells.

There were numerous visits to the clinic for observation, but no improvement was evident. The chest consultant was of the opinion that the lesion was of tuberculous origin, even though acid-fast bacteria were not found. Local injection of streptomycin was advised. In October, streptomycin was injected directly into the lesion in 0.5 gram doses daily for a total of 9.0 grams. There was prompt subsidence in the size of the swelling and the patient was able to breathe easier. It was the consensus of the staff that this effect was due to the streptomycin acting specifically on the granuloma which was of tuberculous origin.

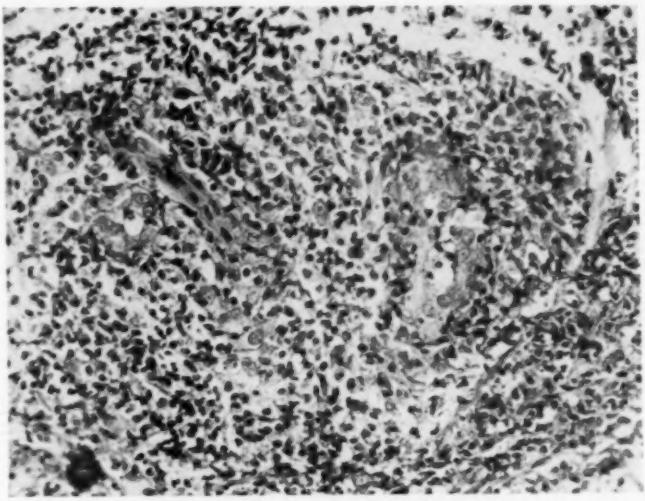

Fig. 10. (Case 6).—Photomicrograph of nasal lesion (X285) showing chronic granulomatous inflammation. In some areas, giant cells and granulomatous epithelioid elements with small tubercle formation can be seen.

He was observed in the clinic and by a private physician with no recurrence of the swelling. Two years later the patient suffered a terminal cerebrovascular accident and was hospitalized. Examination of the nasal lesion at that time showed an adequate airway with no recurrence of the swelling.

Comment. This case was of great interest to the staff because of the tuberculous character of the nasal lesion and the effect of the streptomycin injected locally. Acid-fast organisms were never found but streptomycin appeared to act with the specificity expected usually only in active infection.

Case 7. This white male, age 32, was first seen in the office on July 25, 1955. He gave a history of recurrent pain over the left cheek and in the left nostril for two weeks. This was associated with a feeling of constriction in the left side of the nose and pressure over the left side of the cheek. For the preceding few months he had occasionally blown a large crust from the left nostril. There was no known allergy, and he had never taken antihistamines.

The past history revealed no nose symptoms until 1945, when he experienced pain in the cheek and nose after swimming in a salt water pool while in the Service in the South Pacific. He consulted a flight surgeon who told him that there was nothing wrong. He recovered from this episode, but in the succeeding years he had recurrent attacks of nasal blocking, mainly on the left, and pain over the left cheek. He noticed these symptoms in the preceding three years as occurring particularly in the springtime. He consulted several ear, nose and throat specialists, but they were unable to find anything wrong.

Examination revealed the left middle turbinate covered with a firm and adherent white membrane. When this was scraped loose, the underlying mucosa was very pale. There was no bleeding. Purulent discharge drained from the left middle meatus. The right nasal passage showed no abnormalities. Nasopharyngoscopy revealed purulent discharge on the left posterior pharyngeal wall. The left antrum did not transmit light well on transillumination.

X-rays showed no evidence of sinus disease. Smear and culture showed a pure growth of E. coli and staphylococcus aureus. Slight sensitivity was shown by the organisms to streptomycin, aureomycin, achromycin and terramycin, but resistant to gantrisin, sulfadiazine, erythromycin and penicillin, neomycin and polymixin B. Gram stain showed a few epithelial cells and polymorphonuclear leucocytes, a few gram positive cocci in pairs and rare diphtheroid bacilli.

The patient was placed on achromycin. A biopsy was attempted in the office, but the patient exhibited syncope, and the procedure had to be terminated. He was hospitalized and a biopsy specimen was obtained of the left middle turbinate. The section demonstrated "all the tissue to be inflammatory with no normal epithelium or other pre-existing structures in evidence. The cells present were necrotic leukocytes. In other areas there was a necrotic fibrinous zone beneath which there was inflammatory exudate. This consisted of lymphocytes, plasma cells, rare neutrophiles, and small blood vessels. No fungus structures were present. A few nodular foci of necrosis occurred, but this was not accompanied by cellular features of granulomas which produce tubercles."

A diagnosis of "necrotic inflammatory tissue, etiology not apparent," was made by the pathologist who commented that the biopsy specimen was not diagnostic and that changes present were not those of scleroma. They were more consistent with a necrotising inflammatory disease such as diphtheria, Vincent's angina, agranulocytosis and chemical injury. Diphtheria was excluded by smear and culture.

The blood count showed a leukopenia (4,800) with a relatively normal white cell distribution. The red blood cells numbered 4,700,000 with 14.1 Gm. hemoglobin, and showed no atypical morphological forms. The platelets were normal in number. The Kolmer and Kline tests were both negative,, and the tuberculin skin test was negative.

On Aug. 15, 1955, the patient showed no improvement. His internist suggested administration of meticorten to rule out the possibility of a collagen vascular disease. At the same time he was continued on achromycin to lessen the purulent discharge.

On Sept. 1, 1955, he was hospitalized because of a fever of 105°, purulent discharge from both sides of the nose, right otolgia and the appearance of gray necrotic area over the hard palate to the right of the midline. During his hospital stay, the palate lesion progressed to ulceration and finally perforation into the right nostril. A biopsy specimen of the palate lesion revealed "chronic granulation tissue consistent with a lethal midline granuloma." X-rays of the sinuses at this time showed almost complete opacity of the antra and ethmoids. A Hotchkiss-McManus stain for fungi was done with special reference to histoplasmosis, and this resulted in negative findings; the blood cultures showed no growth. Repeated smears and cultures did not yield any new diagnostic information. Blood sugar was 85 mg. and the non-protein nitrogen was 22. Complete viral studies for murine typhus, Rickettsial pox, Psitt.-LGV group, and Q fever were negative. The patient was given large amounts (1,200,000 units) of penicillin daily along with meticorten and achromycin. His temperature went done to normal, and he felt well enough to be discharged.

One week later on Sept. 28, 1955, he was readmitted because of profuse bleeding from the palate lesion and a daily elevation of temperature to 100° F. and over. It was noted that, in addition, swelling and tenderness was present over the right malar bone. During his hospitalization, recurrent bleeding from the palate was noted, associated with progression of the local lesion. He had a daily spiking of temperature to 103° and over in spite of antibiotics, Cortisone and ACTH. Repeated blood cultures showed no growth. A drop in the white cell count to 2,500 per cubic millimeter with 71 per cent neutrophiles was noted, and a prolonged prothrombin time of 22. The bleeding was controlled by suturing the palate, and the patient was given transfusions of 500 cc. of citrated blood on Nov. 12 and 15, 1955. The fever became more septic and spiking in type, terminating at 105° with his death Nov. 18, 1955.

Postmortem examination revealed the sinus lining to be hyperplastic with a few plasma cells and lymphocytes in the subepithelial layers. The bone of the right antrum was necrotic and surrounded by marked fibroblastic activity and inflammatory exudate. No granuloma or tumor was seen. The liver, spleen and kidneys did not show any granulomata or vascular changes.

Comment. This case exhibited almost total lack of resistance. This was consistent with the microscopic findings of tissue from the right antrum, which exhibited extensive necrosis with virtually no inflammatory exudate. The terminal leukopenia gave added evidence of the total exhaustion of the defense mechanism.

Case 8. A white male, aged 36, was admitted to the Santa Fe Hospital on Nov. 3, 1955, with a history of an upper respiratory infection one year previously, which was followed by a nasal stuffiness on the right side. Bouts of respiratory infections, sinusitis, and purulent nasal discharge recurred during the year. The right nasal obstruction became progressively worse and was associated with occasional bleeding. Except for weight loss of 20 pounds during the preceding year, the history was not significant.

Physical examination showed a thin but otherwise normal male. Temperature was 98.8° F. The right side of the nose was blocked by a friable, irregular mass which bled easily and involved the right side of the septum, the ventral and lateral walls of the nose. Pus was present on

the floor. The impression at the time of examination was that it was more of a granulomatous process rather than neoplastic. X-rays of the sinuses showed thickening of the maxillary sinus mucosa and a smooth polyp on the floor of the right antrum. A smear for scleroma and fungus was taken and later proved negative for both.

The biopsy specimen of the mass was reported as epidermoid carcinoma, Grade 1, although the most striking feature of the section was the marked chronic inflammatory infiltration. Another biopsy was made four days later, which was interpreted as a granulomatous reaction strongly suggestive of Hodgkin's disease. A third biopsy, two weeks later, noted "the pattern of the cells is that of a neoplastic process and is more likely that of Hodgkin's granuloma rather than undifferentiated squamous cell cancer, although the latter cannot be ruled out."

The leucocyte count was 7,400 with 60 per cent neutrophiles, 26 per cent lymphocytes and 14 per cent monocytes. The erythrocyte count was 4,900,000. Culture from the nose showed E. coli. The organism was sensitive to most of the antibiotics except penicillin and polymixin. The Kolmer and Kahn tests were negative.

The patient was placed on streptomycin intramuscularly and achromycin orally. Wyadase was instilled into the left antrum after irrigation. The consultant in charge of the case thought that the "lesion appears more granulomatous rather than neoplastic," even after seeing the pathological studies. He felt that it was a lethal midline granuloma, and advised blood transfusions; however, only one transfusion of 500 cc. citrated blood was given before he was transferred to another hospital for X-ray therapy. The patient was given a total of 1400 *r* through two portals beginning Dec. 29, 1955, to Jan. 10, 1956. The swelling in the nose spread to the face, and the patient showed signs of toxicity. The fever rose irregularly every day, spiking at times to 101°. Antibiotics were resumed, but this did not affect the course of the disease. Necrosis and sloughing was noted over the right side of the nose over the alar cartilages. This spread across the midline to the right side and cheek.

A review of the pathological slides by a pathological consultant was made. It was his opinion that a diagnosis of epidermoid carcinoma was most consistent with the findings.

Patient was readmitted to the hospital on Jan. 22, 1956, when increasing redness of the skin, ulceration and necrosis of the nose and cheeks was noted. The nose was completely blocked by a friable, partially necrotic mass. Purulent discharge drained from the right side of the nose. The lip and eyelids were swollen. The blood cell counts showed a progressive drop in the white cells until it reached a count of 1200 on March 12, 1956, but there was no relative neutropenia. A bone marrow study showed no abnormal findings. One blood transfusion was given with a resulting slight rise in the total cell count. The fever continued septic in character with daily spiking to 102-103°, in spite of antibiotics. The whole face became edematous and subcutaneous hemorrhages obliterated the facial markings. On April 7, 1956, the ulceration extended over the forehead. The white count dropped to 1,000, there was a sustained elevated temperature, and the patient expired on April 8, 1956.

No postmortem examination was performed.

Comment. It was unfortunate that an autopsy could not be obtained to confirm the pathologist's impression of epidermoid carcinoma. The lack of response of this type of neoplasm to X-ray therapy was not unexpected. The associated radia-

tion reaction and secondary infection added to the gross deformity. It would have been of interest to note how the administration of Cortisone would have affected this patient's course.

Case 9. A white woman, aged 25, was seen in the Ear, Nose and Throat Clinic of the White Memorial Hospital on Dec. 12, 1952, complaining of nasal blocking, sore throat, cough and loss of taste of three months' duration. There was an associated irregular fever which, at times, went up to 101° F., preceded by chills and followed by marked perspiration. A recent loss of 20 pounds in weight was noted. Her past and personal histories were not significant.

Physical examination revealed a thin, white woman with an oral temperature of 101° F., pulse 116, and respirations 24, obviously ill. The nose was blocked completely on both sides by red, swollen turbinates and septal mucosa. Purulent material was noted in both sides of the nose, and the posterior choana were blocked by swollen posterior tips of both inferior turbinates. An ulceration in the middle of the hard palate about 0.5 cm. wide with redness and induration of the borders, was noted in the mouth. She was admitted to the hospital with a clinical impression of "Infectious midline granuloma involving the floor of the nose, the septum and the hard palate."

Laboratory tests showed 91 per cent hemoglobin, 4,870,000 erythrocytes and 2,500 leucocytes per cubic millimeter with 68 per cent neutrophiles. A biopsy was made from the palatal lesion and reported as an atypical anaplastic type tumor. X-rays of the sinuses showed increased opacity in the right antrum. Chest X-ray showed no abnormalities. The urine did not show sugar or albumin. Pus was obtained from the right antrum and mucopus from the left antrum. Smear and culture of this material was negative for acid-fast and diphtheria organisms. Sensitivity tests of the isolated organisms showed them to be sensitive to several antibiotics. The blood sugar was within normal limits. Wassermann, Kline and Kahn tests were negative.

Another biopsy (2.5x1.0x0.5 cm.) was obtained, and again a report was made of anaplastic tumor. It was the consensus of the otolaryngological staff that the appearance of the lesion was that of an infectious granuloma of undetermined origin, in spite of the pathological reports.

The patient continued with an irregular daily elevation of temperature. She was placed on streptomycin 0.5 Gm. twice daily intramuscularly. She was also given Vitamin C, 100 mg. and synkovite 10 mg. daily because of the bleeding. The maxillary sinuses were irrigated daily, but pus continued to drain. Because of the difference of opinion regarding the diagnosis, X-ray therapy for the infection was given on three occasions. Terramycin in 250 mg. doses four times daily was added to the other medications with slight improvement shown. She was discharged home.

The nasal discharge and swelling continued, and on Jan. 12, 1953, a Caldwell-Luc procedure was performed on the right maxillary sinus. The sinus was explored without finding any gross infection. The mucous membrane was found to be edematous, but did not contain granulomata or tumor lesions. A specimen of the septal swelling, removed for biopsy, was reported again as anaplastic carcinoma with a great deal of inflammatory reaction. Specimens from the hard palate, maxillary sinus mucosa and turbinates were all reported as being benign. She felt improved after the surgery and was discharged from the hospital.

There followed several other hospital admissions because of frequent

recurrences. At one time a left antrum window was done. At another hospital admission because of increase in the swelling and pain, she was given Cortisone, 25 mg. four times daily, penicillin 300,000 units daily, streptomycin 0.5 Gm., and aureomycin 250 mg. four times daily. The temperature receded to normal, and the patient felt greatly improved.

Two months later the patient was readmitted to the hospital gravely ill and with recurrence of the swelling in the nose. The granulomatous swelling involved the septum, floor of the nose, and both inferior turbinates. It bled easily and pus drained from both middle meatuses and antral windows. The face was swollen with the greatest involvement over the upper lip, nose, cheeks and lower lids. The temperature was elevated, sometimes rising to 104° F., and the patient complained of severe pain over the face and also of headaches.

The blood count now showed the leucocyte count to be 2,200 per cubic millimeter with 63 per cent neutrophiles (14 band cells). Culture of the pus from the nose yielded staphylococcus albus.

The patient was placed on the critical list. Because of the continued leukopenia and apparent lack of resistance to infection, it was decided to administer blood to the patient. Improvement was noted after the first pint of blood was given. Daily transfusions of 500 cc. of blood followed for three days. The general improvement was marked. The temperature subsided to normal and the swelling of the face receded in the next three days. The blood count now showed the leucocytes 5,000 per cubic millimeter with 58 per cent neutrophiles and a few band cells present. She was discharged from the hospital and continued to improve at home. Two more transfusions were given in the following month with apparent acceleration of the healing in the nose and palate. Four months later the nose was completely healed, and she was breathing well. The leucocyte count remained at 5,200 per cubic millimeter with a normal distribution ratio.

The patient has been observed regularly since, particularly for the upper respiratory infections. She has had one pregnancy with delivery of a normal child since that time. When last seen, now approximately five years since her grave illness, she seemed to be in excellent health.

Comment. This patient exhibited the typical findings and appeared to pursue the same clinical course as the so-called "lethal midline granuloma" cases. Supportive therapy and alertness in detecting causative factors would seem to offer the greatest hope in these cases. This case illustrates the varied causative factors that may produce lesions resembling the lethal type. In this case, it was possible, fortunately, to discover and counteract the poor resistance to infection exhibited by this patient with blood transfusions. One may postulate that the relentless destruction seen in some cases of lethal midline granuloma may be a manifestation of lack of resistance to even minor infections.

CONCLUSIONS.

This study is based upon a review of nine cases diagnosed

TABLE I.

	Sex	Race	Age of Onset	Duration	Area of Involvement	Preliminary Diagnosis	Treatment	Final Diagnosis	Final Result	Last Seen
Case 1 (F.N.)	M	W	33	13 mos.	Palate, nasopharynx	Lethal midline granuloma	Antibiotics, Cortisone, *X-ray therapy*	Lymphoepithelioma	Cured*	6 years later
Case 2 (M.H.)	F	W	27	10 mos.	Palate, nose	Lethal midline granuloma	Antibiotics, antimony, iodides	Transitional cell carcinoma	Died—autopsy	
Case 3 (E.S.)	M	N	34	6 mos.	Palate, floor of nose	Lethal midline granuloma	Antibiotics, *ACTH and Cortisone*	Collagen disease, type (?)	Cured	6 mos. later
Case 4 (J.P.)	M	W	42	8 mos.	Gums, sinuses, dura, kidneys, nose	Lethal midline granuloma	Antibiotics, ACTH, Cortisone	Wegener's granuloma	Died—autopsy	
Case 5 (G.T.)	M	N	72	40 mos.	Soft palate, nasopharynx	Lethal midline granuloma	Antibiotics, X-ray therapy, iodides	Ackermann verrucous carcinoma	Died—no autopsy	
Case 6 (S.H.)	M	N	62	6 mos.	Nose	Lethal midline granuloma	*Streptomycin* injected locally	Tuberculoma of nose	Cured	2 years later
Case 7 (L.H.)	M	W	32	4 mos.	Nose, palate, bones face	Lethal midline granuloma	Antibiotics, ACTH, blood transfusions	Osteomyelitis face bones(?); lethal midline granuloma (?)	Died—autopsy	
Case 8 (E.T.)	M	W	36	16 mos.	Nose, face	Epidermoid carcinoma or lethal midline granuloma(?)	Antibiotics, X-ray therapy, blood transfusions	Epidermoid carcinoma(?) Lethal midline granuloma(?)	Died—no autopsy	
Case 9 (B.C.)	F	W	25	6 mos.	Palate, nose	Lethal midline granuloma(?)	Antibiotics, *blood transfusions*	Blood dyscrasia	Cured	5 years later

*NOTE: "Cured" is used in the sense that the patient recovered and has not shown signs of recurrence since last seen. (Apparent effective therapy italisized.)

as lethal midline granuloma. Three of the cases were encountered in private practice, while the other six were found as a result of a survey of clinic patients at the Los Angeles County Hospital, White Memorial Hospital and Santa Fe Hospital. The diagnosis of lethal midline granuloma was established in all the cases after routine clinical and laboratory studies excluded other possible causes; however, after continued observation and study it was possible, in five of the nine cases, to establish a definite diagnosis. Of these, four cases survived and were returned to normal health. The specific diagnoses established included neoplasm in three of the cases, tuberculoma in one case, and blood dyscrasia (leukopenia) in the other case (see Table). Only two patients were over 45 years old, and men predominated seven to two.

As a result of this study, I believe that the gross clinical description known as lethal midline granuloma can be produced by a variety of mechanisms. We are all familiar with similar ulcerative necrosis produced by the specific granulomata, blood dyscrasias and infections such as osteomyelitis and others. This may be a manifestation of poor resistance to infection. It can also be produced by some neoplasms which may have common histological features. There is also intriguing theoretical and experimental evidence that a vascular necrotizing mechanism related to the collagen diseases may be a basis for this type of lesion.

At the present time, lethal midline granuloma represents little more than a general term for a number of conditions causing tissue ulceration and destruction whose fundamental character and pathogenesis is still poorly understood. With pathognomonic criteria absent, both clinically and histologically, one may question whether lethal midline granuloma can be justified as a pathological entity except as a tentative diagnostic expedient. At best, it serves as a wastebasket for conditions difficult to recognize. At worst, the chief danger of complacently accepting this diagnosis is that it may mask a specific disease process until it is too late for effective treatment.

It is anticipated that with our increasing knowledge of tissue changes under stress phenomena, or as yet unknown

mechanisms, this clinical diagnosis will be removed from the group described in terms of gross appearance and behavior and placed in a more precise etiological category.

As clinicians, our aim in the management of these cases is twofold: diagnostic and supportive.

The persistence in diagnostic investigation of these cases, in spite of discouraging and sometimes hopeless odds, may spell the difference between success or failure. Systemic and repeated attempts to rule out those conditions which may be masked by the lethal midline granuloma clinical picture is imperative.

As was stated previously, it was our experience that a neoplastic process may be masked by inflammation and necrosis. This is particularly true in the case of the lympho-epithelial group which is often found in this region. Cortisone and antibiotics may play an added role in abolishing the inflammatory reaction, thus allowing the neoplasm to be recognized. The ultimate value of Cortisone is still to be appraised in the future as more experience with this drug is gained.

The lack of normal resistance mechanisms is characteristic of these patients. It is generally recognized that they are usually sicker than they realize. Supportive measures to help stimulate and sustain resistance is of utmost importance. The longer these patients are kept alive in a relatively good state, the better the chances for ultimate recovery. Proper dietary intake, measures to combat anemia and leukopenia by medication and blood transfusions should be instituted promptly when found. The value of blood transfusions is well illustrated in cases where it proved life-saving.

It is encouraging that the new concepts relating to tissue immunity responses, stress phenomena and the collagen diseases have opened a new door for promising investigation and offer new hope of answering many questions.

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LARYNGOFISSURE IN THE TREATMENT OF LARYNGEAL CARCINOMA.

A Critical Analysis of Success and Failure.*

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INTRODUCTION.

Laryngofissure has been used for many years as a method of treatment for selected cases of laryngeal carcinoma (Howie[1]; Thomson[2]). It has produced gross five-year survival rates varying from 59 to 87 per cent (Schall[3]; Wang and O'Donnell[4]; Marchetta, et al.[5]; and Jackson, et al.[6]). Restated, this means that laryngofissure fails to control the cancer in from 13 per cent to 41 per cent of the cases. What are the factors that account for the failure of this therapeutic modality? The purpose of this paper is to evaluate critically factors associated with success or failure of laryngofissure in the treatment of carcinoma of the larynx. These data are not available in the literature to our knowledge.

MATERIAL AND METHODS.

All coded cases of carcinoma of the larynx treated by laryngofissure during the period 1939 to 1954 were selected from our files. These are consecutively accessioned cases that represent the combined experience of a group of otolaryngologists at McMillan Hospital. The clinical histories, pathological protocols, and microsections were carefully reviewed. The paraffin blocks were recut whenever the available microsections were not of good quality.

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Of the original 84 coded cases five were discarded because on review of the tissue sections no evidence of carcinoma was seen. Four of these five patients are alive for more than five years. The remaining patient died of heart failure three years after laryngofissure. Thus, a group of 79 cases with authenticated epidermoid carcinoma of the larynx were left for study. The age and sex distributions are shown in Table I. The difference between the median ages for males and females, 60 and 49 years respectively, is statistically significant, ($X^2 = 5.7$. $P < .02$).

Our criteria for the evaluation of laryngofissure as a method for treating intrinsic* epidermoid carcinoma of the larynx are as follows:

TABLE I.

Age Distribution by Decades of 79 Patients Treated by Laryngofissure.

	IV	V	VI	VII	VIII
Male	2	7	28	24	9
Female	3	1	3	2	0

The operation is considered a success if:

1. Laryngofissure was the only definitive therapeutic procedure.
2. The patient is alive five years or more without evidence of persistent carcinoma.
3. The patient died in less than five years, was necropsied and no persistent carcinoma found (We would exclude those patients dying in the immediate postoperative period).
4. The patient died five years or more after treatment without evidence of persistent carcinoma.

It is considered a failure if:

1. Subsequent irradiation therapy or surgery were employed.

*The term intrinsic is used to define a carcinoma limited to a mobile true vocal cord that does not involve the anterior commissure or the subglottic area.

2. Persistent carcinoma was demonstrated by biopsy.
3. The patient died of carcinoma of the larynx.
4. The patient died in less than five years without being necropsied.
5. The patient was lost to follow-up.

RESULTS.

In this study 45 cases, 57 per cent, satisfy the criteria for success. *Thirty-nine* of these patients are surviving from five to 18 years; *three* died of other causes five, eight, and 16 years respectively after fissure; *three* died one, one-and-one-half and seven years, respectively after fissure, and at autopsy no residual carcinoma was found.

Thirty-four cases, 43 per cent are classified as failures. *Ten* of these are surviving five or more years after laryngofissure without evidence of tumor; six of the ten survivors had subsequent laryngectomies, three irradiation therapy and one both irradiation therapy and laryngectomy; *one* patient died six years after fissure and irradiation therapy without clinical evidence of tumor; *twelve* individuals died of carcinoma of the larynx. Six of these twelve received further therapy, either surgical, radiotherapeutic, or both; these deaths occurred from less than one year to eleven years after fissure.* *Seven* patients died in less than five years without autopsy; three patients were lost to follow-up; one of the patients presently lost to follow-up is known to have had biopsy proven persistent tumor in the neck five months after fissure.

When the series is divided into two groups, the cases from 1939 to 1947 (Group A), and from 1948 to 1954 (Group B), 33 and 46 patients are in the groups respectively (see Table II). Applying the above criteria, figures of 39 per cent for success and 61 per cent for failure are derived for Group A;

*Two patients who died of carcinoma lived for four and six years respectively, after fissure without clinical evidence of cancer; they then presented with carcinoma involving a contiguous portion of the larynx and died eleven and eight years after fissure. It is possible that these are cases of secondary primary tumors. We can not prove this and, therefore, they are classified as above.

70 per cent for success and 30 per cent for failure in Group B. In Group A, 27 per cent (9/33) of the patients treated eventually died of laryngeal cancer, whereas in Group B only 7 per cent (3/46) of the patients died of cancer. The salvage of patients with incompletely excised or persistent carcinoma increased from 9 per cent (3/33) in Group A, to 20 per cent (9/46) in Group B. It is important to realize that these salvaged cases do not fulfill our criteria for success.

In an attempt to evaluate the objective findings associated with success or failure of laryngofissure the clinical de-

TABLE II.

Results of Laryngofissure, 1939 to 1954.*

	Group A (33 patients) 1939-1947	Group B (46 patients) 1948-1954	Total (79 patients) 1939-1954
1. Alive > 5 years without further treatment	33	61	49
2. Died < 5 years with autopsy	0	7	4
3. Died > 5 years without further treatment	6	2	4
4. Alive > 5 years with further treatment	10	16	13
5. Died < 5 years without autopsy	12	7	10
6. Died of cancer	27	7	15
7. Lost to follow-up	12	0	5
Success 1, 2, 3	39	70	57
Failure 4, 5, 6, 7	61	30	43
Success 1, 2, 3, 4	49	86	70
Failure 5 and 6	39	14	25
Indeterminate 7	12	0	5

*All figures are simple percentages rounded to the nearest whole number.

scriptions of the laryngeal lesion and pathological data were reviewed. Unfortunately, the clinical descriptions were inadequate for detailed tabulation and analysis. The analysis and statistical significance of the pathological data are shown in Table III.* The differentiation of the carcinoma, invasion of the intrinsic muscle, and extension of tumor to a margin of excision are all significant observations when correlated with outcome; these factors are elaborated upon in the discussion.

*The seven patients who died in less than five years without autopsy or clinical evidence of cancer are considered indeterminate for these comparisons and deleted prior to the calculations.

Extension of carcinoma *in situ* to a margin of excision is not significant.

The nine women represent 11 per cent of the series, approximately the same incidence reported in other series. Six are alive and well without tumor from seven to 18 years after fissure; one died seven years after fissure, and at autopsy no tumor was found; one is alive 11 years after fissure, having had a laryngectomy, and one died of cancer three years after fissure and irradiation therapy.

TABLE III.

Correlation of Pathological Findings and Outcome.

	Outcome (Number of cases).					
Differentiation	Success*	Failure*	Total	Per Cent Favorable	X^2	P
Pathologic Findings.						
Well	31	11	42	74	4.87	<0.05
Moderate and Poor	8	15	23	35	12.1	<0.01
In situ carcinoma, only	6	1	7	86	1.1	>0.2
Tumor at the margin	5	16	21	24	20.0	<0.01
Muscle invasion	9	12	21	43	5.4	0.02

*As defined in the text.

Seven cases of carcinoma *in situ* (intraepithelial carcinoma) are included in this study. We define this lesion as one in which the entire thickness of the epithelium is carcinomatous and submucosal invasion absent. Four patients are alive and well from six to 11 years without evidence of carcinoma; one died one-and-one-half years after fissure, and at autopsy no tumor was found; two died of laryngeal carcinoma at five months and nine years, respectively.

DISCUSSION.

The evaluation of a mode of therapy in the treatment of cancer is dependent upon many factors, among them being the selection of cases, skill in the execution of therapy, thoroughness and accuracy of pathological evaluation and valid analysis of the end result. The lack of these leads to misconceptions, often perpetuated, that are detrimental to and, in fact, at times fatal for patients. If the results of laryngofissure for our original 84 patients are accepted at their

face value, *i.e.*, without review of the pathological findings, failures as only those dead of carcinoma and discarding the patients lost to follow-up, the five year success-rate would be 86 per cent for the entire series! By eliminating the five cases that are not histologically acceptable to us, and applying the criteria for success and failure listed previously, we arrive at the success rate reported (see Table II).

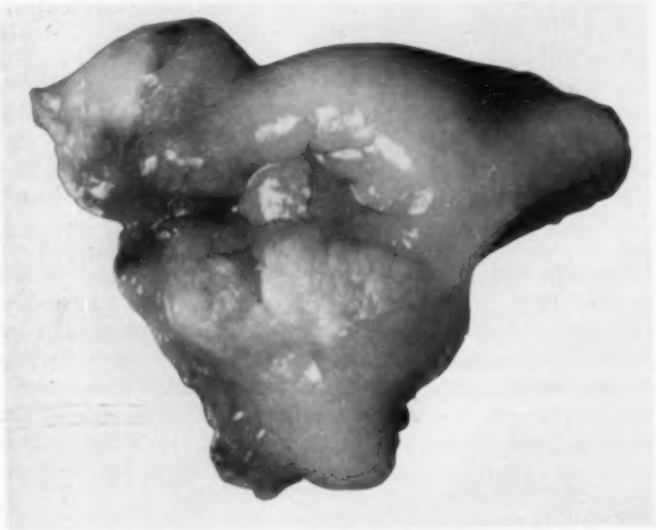

Fig. 1. Laryngofissure specimen, in a single block, encompassing a well differentiated carcinoma of the vocal cord. (Enlarged approximately two times). W.U. Neg. No. 58-5080.

The ideal laryngofissure will include *in a single block*, the true and false cords, the ventricle, the vocal process and a small area of the subglottis (see Fig. 1). Refinements in operative technique have led to the inclusion of the entire anterior commissure and a portion of the anterior third of the opposite true vocal cord. Knowing this, and being cognizant of the lymphatic drainage of the vocal cord, automatically defines the limits of carcinomas suitable for treatment

by laryngofissure. It is not uncommon for a carcinoma to be more extensive when examined histologically than is clinically appreciated. The number of patients with marginal involvement by carcinoma in our series, and the high degree of correlation of this finding with failure, is indicative that these patients were either improperly selected or that the fissure was inadequate—if the cancer was actually limited to the area ideally encompassed by a laryngofissure.

Invasion of the intrinsic muscle gives a most pessimistic bias as to outcome. Only 24 per cent of patients with this finding were treated successfully in this series (see Table III). This finding is usually, though not always, heralded by impaired mobility of the true vocal cord. Again, the acumen of the laryngologist is taxed, and though some cases with muscle invasion are successfully handled by laryngofissure, careful consideration of the high chance of failure should be given before this method of therapy is employed.

The differentiation of the carcinoma must also be considered. Well differentiated cancers are treated successfully in 74 per cent of such cases in our series. Moderately and poorly differentiated cancers, however, are controlled by laryngofissure in only 35 per cent of such cases in our series. The designation of the differentiation of these carcinomas is a factor dependent upon the pathologist. He must examine the biopsies with care and cognizance of what his diagnosis will mean.

The functional result of the larynx that has been treated by laryngofissure must be considered in the evaluation of the procedure. The patient can breathe through his larynx in the majority of instances; however, the incidence of postoperative "granulomas", stricture and membrane formation is not negligible (LeJeune and Lynch[7]) and does necessitate further surgical intervention. Two patients in this series have permanent tracheotomies because of laryngeal stenosis. Interference with swallowing is rare. Post laryngofissure patients do have a voice, but one that is hoarse. In effect, the functional result in relation to voice is something less than desirable. It is a fact that carcinomas of the vocal

cord amenable to laryngofissure are responsive to irradiation therapy, as indicated by reports of Wang and O'Donnell,[4] Schall,[3] and Harris et al.,[5] who have 80 per cent, 92 per cent and 88 per cent five-year survivals. The functional result with this type of therapy is good.

It will be noticed that five cases with "tumor at the margin" in Table III are successes for laryngofissure. In addition, two cases classified as failures had "no tumor" in the fissure. These contradictory findings are explicable. The methods of sampling the fissure specimen for histologic evaluation varied during the period studied. Until recent years they may be criticized for having been not only haphazard but also incomplete. These are the faults of the pathologist. In some instances they have led to laryngectomy in which no tumor was found. The laryngologic surgeon who employs laryngofissure must realize the importance of removing the specimen as a single block, orienting it with care and conferring with the pathologist. The entire specimen should then be step-blocked and sectioned. If tumor approaches any margin, that block should be sub-serially sectioned. In this manner, as is currently in use in our laboratory, accurate statements may be made and further therapy, if necessary, based on the best information. The lack of such cooperation and exacting examination probably accounts for the paradoxes in Table III.

Twenty-one cases had tumor at a margin of excision. Of these 12 had no further therapy, and nine had either laryngectomy or irradiation therapy. Of the 12 having no further therapy, five are alive and well, five died of cancer and two died in less than five years of other causes without clinical evidence of cancer. Of the nine who had further therapy, five are alive and well; two died of cancer, one dicd in less than five years without evidence of cancer, and one is lost to follow-up. Statistical analysis of these data show no significant difference between the "treated" and "not treated" groups. Thus, from the review of these cases we are unable to give an objective answer to the question a surgeon might ask, "What do I do when there is tumor at a margin?" It is our opinion, however, that after the type of pathological ex-

amination we advocate when tumor is at a margin of excision, irradiation therapy should be used rather than resorting to laryngectomy.

CONCLUSIONS.

1. A review of the clinical and pathological data from 79 patients having had laryngofissure for carcinoma of the true cord reveals an overall success rate for the procedure as 57 per cent.

2. The degree of differentiation of the carcinoma, the presence of tumor at the excisional margins, and invasion of the intrinsic muscle are pathological features that are significantly related to the failure of this technique.

3. Sucess of laryngofissure is dependent upon careful selection of candidates for the procedure, *en bloc* removal of the specimen so as to encompass the lesion, and careful pathological examination and interpretation.

4. From analysis of the data no meaningful statement regarding future therapy in those cases with "tumor at the margin" can be made.

5. Periodic follow-up examinations of post-laryngofissure patients should never cease because of the late appearance of persistent tumor and possible second carcinomas.

6. Because the survival rates of patients with intrinsic laryngeal carcinoma treated by irradiation are as good as, if not better, than those treated by laryngofissure, and because the functional result in terms of voice is better after irradiation therapy, it would seem that irradiation should supplant laryngofissure as the therapy of choice.

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SCHOLARSHIPS FOR NASAL SURGERY COURSE.

The American Rhinologic Society provided full scholarships to five Mexican physicians, and half scholarships to six, to enable them to attend a course in reconstructive nasal surgery presented at the White Memorial Hospital, Los Angeles, January 9-16, 1959.

Dr. Amos E. Friend of Manchester, Conn., chairman of the Society's Public Relations Committee, said the scholarships were designed to further cement international relations as well as to spread surgical knowledge.

THE PRESCHOOL NERVE-DEAF CHILD.

Study of Etiological Factors.*

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The purpose of this thesis is to present the results of a study of 328 children with severe hearing loss, examined by the author during the years 1949 to 1952, at the Clinic for the Deaf Child of the Winthrop Foundation for the Study of Deafness at the Massachusetts Eye and Ear Infirmary. The aim of the study was to determine the causes of deafness of these preschool deaf children. The pertinent available literature will be reviewed.

The Clinic for the Deaf Child of the Winthrop Foundation was established through the foresight of Drs. LeRoy A. Schall and Harold D. Walker in 1940. The purposes, scope, organization and accomplishments of this clinical research program have been reported by Guilder, Guilder and Schall, Meltzer and Lewis. The author is grateful to Drs. Schall and Meltzer for the opportunity given him in 1949 to direct the Clinic for the Deaf Child for several years, and thus to be intimately associated with an inspiring group of youngsters and their parents, and a devoted group of co-workers.

REVIEW OF THE LITERATURE.

Etiological Factors.

In recent years there has been a great increase in interest in the preschool child handicapped by deafness, and numerous excellent papers and books have been written on the subject. Our concepts as to the etiology of deafness present at birth (previously often loosely labeled as "hereditary" or "congenital") or acquired in early life are changing, especially since the monumental discovery by Gregg of the significance

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of the rubella virus as a cause of congenital defects including deafness; and by Goodhill, of the significance of the Rh factor as a cause of nuclear deafness. Goodhill has stated, "The recent discovery that rubella (German measles) in the mother during the first trimester of pregnancy might cause deafness in the child was the first major contribution to the etiologic analysis of infantile nerve deafness in the present century." Goodhill's work represents another such contribution.

Congenital Deafness.

Kinney, Goodhill, Fowler and Van Egmond have emphasized the ambiguity of the term "congenital," and the tendency in recent otological literature has been to discard it. Formerly the term *congenital* has often been used as equivalent to hereditary. Van Egmond points out the following three possibilities:

1. Deafness may be congenital but not hereditary, as in deafness caused by rubella during pregnancy.

2. Deafness may be hereditary but not congenital, as in otosclerosis.

3. Deafness may be congenital and hereditary as in sporadic recessive deafness.

Goodhill has classified infantile deafness into:

1. Hereditary (gene transmitted).

2. Acquired—

A. Prenatal (infections, acquired developmental anomalies, drug intoxications).

B. Natal (birth injuries and erythroblastosis fetalis).

C. Postnatal (meningitis, viral acoustic neuritis, encephalitis and miscellaneous).

Fowler has classified the "congenital" causes of deafness as:

1. Causes during preconception.

2. Causes during pregnancy.

3. Causes during labor.

1. Hereditary Deafness.

According to Van Egmond there are two types of hereditary deafness, namely *dominant inner ear deafness* and *recessive sporadic deafness.*

a. Dominant inner ear deafness usually develops at middle age and is progressive; it is rarely congenital; however, he cites the work of Waardenberg, who in 1951 described a hitherto unknown hereditary syndrome of six chief characters, one of which was congenital dominant deafness (present in 20 per cent of the cases).

b. Recessive sporadic deafness is the common form of inherited deafness in man. Because the gene for deafness is transmitted as a recessive characteristic, consanguinous marriages have a profound effect on its incidence. This fact was noted by Fay in 1889, long before the laws of inheritance were known.* Ballenger reports that 47 marriages between blood relations produced 72 deaf mutes. Hopkins et al., made an extensive study of 310 pedigrees at the Clarke School for the Deaf. They found that the incidence of cousin marriages among the families of the deaf children was about 8 per cent as compared to 0.2 per cent in the general population. The excellent and detailed reports on heredity and consanguinity by Shambaugh and Yearsley are worthy of study.

The incidence of hereditary deafness is difficult to ascertain from the literature, as the percentages vary greatly, and undoubtedly numerous cases of acquired deafness have been erroneously labeled hereditary in past statistical reports.

Thus, Van Egmond states that "the number of cases of congenital deafness by heredity is presumably half to one third of all the deaf, recessive deafness strongly predominating. According to Dahlberg two-thirds of the congenital deaf would be deaf by heredity." Beasley, reporting the results of a survey of the schools for the deaf by the United States Public Health Service, states that the deafness in 61

*See also the interesting paper by Alexander Graham Bell (1883)—"Memoir Upon the Formation of a Deaf Variety of the Human Race." Reference No. 156.

per cent of the children was labeled congenital, and in 41 per cent of these "congenital" cases it was labeled hereditary. Carruthers (1945) cites Fraser, who in 1922 analyzed the histories of 135 deaf mutes at the Edinburgh Royal Institution for Education of the Deaf and Dumb. Of these, 75 were classified as congenital deaf mutes and 60 as cases of deaf-mutism acquired in early life. In only 24 of the congenital deaf mutes was there any possibility of a hereditary factor. That left 51 cases in which some extraneous cause was responsible. These figures agreed with the quoted figures of numerous other investigators quoted by Fraser: that slightly over 50 per cent of cases of deaf-mutism are congenital and about 30 per cent of these are hereditary (or about 15 per cent of the total).

On the other hand, Bordley (1952) reported an analysis of etiologic factors underlying impaired hearing in 485 preschool deaf children. He found familial deafness in only 18 of these children (less than 4 per cent). Fowler reported 81 children with prenatal causes of deafness out of 270 deaf young children. Of the 81, only 10 were ascribed to "causes during preconception," (seven hereditary deafness, one with retinitis pigmentosa, and two with syphilis), an incidence of 3.7 per cent of the total (10/270).

Kerr Love wrote in 1921: "The thing most wanted from the pathologist at present is a series of postmortem examinations of undoubtedly deaf-born children." Carruthers adds that "This is still true in 1944." Kinney reported in 1950 that following a complete survey of all published volumes of the *Cumulative Index Medicus* he found 42 articles on the subject of hereditary deafness; however, he was unable to find a single human case in which there was an accurate history and acceptable hearing tests combined with pathological study of both the temporal bone and brain. "There is not one American case. This is a very shocking condition, and I would urge that effort be put forth to obtain such specimens from cases that might be within our knowledge." He suggests that a central repository of such case histories and specimens be established by the American Otological Society.

Altmann (1950) made a very scholarly, comprehensive re-

view of the otolaryngological literature on the histologic picture of inherited nerve deafness in man and animals, and he reports two cases of his own. This work is a classic and will certainly facilitate research in the future. He concludes that "the anatomic findings in inherited deafness can be divided into two types:

1. Primary changes in the cochlear duct and saccule: *a.* changes confined to the epithelial parts of the cochlear duct with or without involvement of the saccule (so-called sporadic deaf-mutism in man, deafness in dogs and cats with pigment anomalies, deafness associated with locomotor anomalies in rodents); *b.* additional slight anomalies of the osseous framework of the cochlea (in man); and *c.* marked anomalies in the membranous and osseous parts of the cochlea, the saccule, the endolymphatic duct and sac (so-called typus Mondini in man and dogs). In all the subgroups, particularly the last-named one, coordinated anomalies of the central cochlear system might be present.

"*2.* Primary degenerative atrophy of the spiral ganglion on the basis of an inherited 'localized weakness of the cochlear system (man, horses)."

2. Acquired Deafness—

A. Prenatal Causes—*1.* Maternal rubella. Cases

In 1941 Gregg, an ophthalmic surgeon in Sydney, New South Wales, reported a marked increase in the number of cases of congenital cataract and heart lesions in children of mothers who had rubella during the first trimester of pregnancy. This followed a pandemic outbreak of rubella in Australia in 1939 and 1940. He suggested that rubella contracted by mothers during the first trimester was the direct cause of congenital cataract and other defects. As Wilson points out, he was deservedly honored with a knighthood for his monumental discovery.

Goodhill, in an excellent study of the nerve deaf child has reviewed the history of rubella observations by Australian, British and American authors. Following Gregg's published report, a number of articles appeared from Australia in

which cardiac lesions and deafness were reported as important sequellae. Among these were the reports of Swan et al., Carruthers, Welch, Martin, Evans, Murray and Hiller.

Gregg (1946) reported an incidence of 111 cases of deafness, 38 with heart disease, and 23 with eye defects in 130 cases of rubella. Swan et al., (1946) gave a detailed analysis of the sequellae of maternal rubella. These included cataracts, deaf-mutism, heart disease, microcephaly, umbilical hernia, bifid uvula, mental deficiency, speech defects and strabismus.

Murray (1949) made a thorough study of 105 rubella-deaf children. He found no difference in the degrees of deafness when the rubella was contracted at six weeks and at three months. Most of these children were only moderately to severely deaf but not totally deaf, with an average loss over the speech range of 65 db. in the better ear. They can be benefited by the use of hearing aids. He, therefore, deplores the use of the term "deaf-mute" for these children. In the same year, Hiller studied 42 congenitally deaf children. Of these, 32 were of rubella origin, and had audiometric findings similar to those reported by Murray.

In 1946 Martin reported 36 cases of deafness due to maternal rubella out of 102 deaf children studied. The rubella was presumably contracted during an epidemic in Britain in 1940 and 1941.

Among American authors, Goodhill (1950) notes the following: Reese, Erickson, Altmann and Dingman, Hopkins, Ober et al., Aycock and Ingalls, Fowler, and MacFarlan.

Ober, Horton and Feemster reported (1947), 17 abnormal pregnancies in a study of 54 mothers who had rubella in 1943 in Massachusetts. Of the 17, abortions occurred in nine, and the other eight produced infants with abnormalities.

Aycock and Ingalls emphasize the seriousness of maternal rubella as a cause of disease in infants. They suggest the possibility that other virus diseases, including poliomyelitis, may be the cause of many fetal diseases and developmental anomalies.

MacFarlan (1948) emphasized that "recent investigations

show that rubella in the pregnant mother is a frequent cause (of deafness) even though the attack may be mild."

Lemmon (1950) stated that if a woman contracts rubella during the first 100 days of pregnancy, the chances are one in four the offspring will have some severe congenital defect. Landtman (1948) felt that other diseases, including the common cold, influenza, and pneumonia, may have a similar effect.

The percentage of cases of deafness in infancy caused by rubella is variable. This may be due to the fact, stressed by Goodhill, that the earlier reports emphasized the cardiac and ocular lesions and were made while the childrn were still too young for careful audiological evaluation. The later statistics "show clearly that deafness was by far the most common sequel of maternal rubella, and that congenital cataract and congenital cardiac disease were relatively infrequent sequellae."

As noted above, Martin reported an incidence of 35 per cent in his study of 102 deaf children in Britain. Of 147 cases with congenital lesions, Carruthers (1945) found 80 per cent (116) were severely deaf. Of 102 cases with a definite history of maternal rubella, 74 were deaf and 14 have congenital heart lesions.

Goodhill (1950) found that of 904 deaf children studied, maternal rubella in the first trimester of pregnancy was the potential cause of deafness in 186 (20.5 per cent), as against 3 per cent caused by erythroblastosis and 10 per cent caused by meningitis.

In Bordley's report (1952), maternal rubella is shown to be the cause in 24 out of 485 cases (5 per cent), as against 29 cases caused by erythroblastosis and 49 cases due to meningitis. Fowler and Basek (1954) report 12 cases of maternal rubella out of 270 cases (4.5 per cent, as against 12 cases due to the Rh factor, and 10 cases due to meningitis.

The pathology in the temporal bones in rubella deafness has been discussed by Carruthers (1945), Swan (1949), Schall, Lurie and Kelemen (1951), Nager (1952), Lindsay

et al. (1953), and Lindsay and Harrison (1954) and Wilson (1955).

Rubella, and possibly other infectious or toxic agents, attacks that part of the embryo which is most actively developing at the time of infection. "It is recognized that above all, the timing of the interference is the vital factor. The same type abnormality is producible by several methods experimentally providing they are applied at the same developmental stage, and it thus appears that for each part of the body there is a time, its critical developmental period, at which it would be selectively affected by any one of many methods though in varied degree" (Lindsay). Swan (1949) found that the average period of pregnancy for congenital cataract was 1.4 months, for heart lesions 1.5 months, and for deafness 2.3 months. Murray (1949) points out that the inner ear appears to be most easily damaged between the sixth and twelfth week.

Lindsay and Harrison (1954) state that though the amount of pathological material is small, a comprehensive picture of the histo-pathology of this condition has emerged. They find that rubella in the first trimester produces in the child the sacculo-cochlear (Scheibe) type of malformation of the inner ear similar to the hereditary type, with the greatest defects noted in the apical coils. The bony labyrinthine capsule is always normal, as are the cells of the spiral ganglion and the nerve fibers, utricle and semicircular canals.

B. Natal Causes—1. Erythroblastosis Fetalis.

The establishment of a definite relationship of kernicterus and erythroblastosis with bilateral nuclear deafness by Goodhill in 1949 was a great advance in the search for the etiological factors of nerve deafness in early childhood.

In 1875 Orth first noted the relationship of severe jaundice in new-born infants with the postmortem yellow pigmentation of certain nuclear masses of the brain. To this pathological staining Schmorl applied the term "Kernicterus" in 1903.

Zimmerman and Yannet, in 1933, pointed out that "jaun-

dice of the nuclear masses of the brain is most frequently, if not exclusively, associated with icterus gravis neonatorum."

In 1940, Laudsteiner and Wiener discovered the Rhesus factor in human red cells. This was a new agglutinogen (protein) on the surface of human red cells (also present in the Rhesus monkey, hence: "Rh") found in 85 per cent of the white population, and inherited according to Mendelian law as a dominant characteristic.

In 1941, Levine, Katzin and Burnham pointed out that incompatibility between the Rh antibodies in the mother's serum and the Rh factor in the red blood cells of the newborn infant was the cause of the mysterious, and often fatal, group of diseases known as "erythroblastosis fetalis" (including "hydrops fetalis," icterus gravis neonatorum, and congenital hemolytic anemia). Lucid summaries of the relationship between erythroblastosis and the Rh factor can be found in the excellent articles by Diamond, Goodhill, and Cavanagh.

In 1944 the first case of severe deafness following kernicterus was reported by Coquet. In 1948 Landy reported four cases of deafness among eight cases of kernicterus.

In 1950 appeared two articles by Goodhill. He pointed out that "one of the sequellae of Rh factor incompatibility namely, erythroblastosis with kernicterus, may result in a bilateral perceptive deafness and other physical defects, the most common of which is athetoid spasticity." He found that of 904 deaf children studied, erythroblastosis was the potential cause of deafness in 3 per cent of the cases, as against 20.5 caused by maternal rubella and 10.3 per cent by meningitis. He concludes that "the Rh factor thus takes its place in the etiologic classification of infantile preceptive deafness. This position is not a major one. It does not approach maternal rubella, meningitis and the exanthemata in numerical importance. It is nevertheless, a significant cause and one which may point to other serologic factors in the etiology of infantile deafness."

In 1950 Barnett and Ryder published a report of one case which recovered from erythroblastotic kernicterus but had as one of its sequellae total deafness. They state "to the best

of our knowledge, deafness has never been described as one of its sequellae," being apparently unaware of the above-mentioned reports.

In 1950 Evans and Polani reported on 16 patients with neurological sequellae of erythroblastosis, of which five are deaf (30 per cent). Crabtree and Gerrard (1950) reported 16 cases of perceptive deafness in 20 cases of kernicterus (80 per cent). Pearlstein (1950) reported that deafness is a common sequel of kernicterus, occurring in 40 per cent of cases.

In 1952 Johnson found among 50 cases of nerve deafness six cases probably due to Rh incompatibility. In the same year Gerrard wrote an excellent summary of kernicterus and pointed out the frequency of deafness as a sequel. Bordley (1952) reports erythroblastosis as a causative factor in 29 out of 485 cases of preschool deaf children (6 per cent).

Kinney (1953) reports 14 cases out of 630 children with partial perception deafness (2.2 per cent) caused by erythroblastosis. Fowler and Basek (1954) found an incidence of 12 cases due to the Rh factor out of 270 cases (4.5 per cent). Cavanagh (1954) published an excellent review of "The Rhesus Factor in Deafness." She found three cases of Rhesus sensitization among 118 deaf children. Among 124 Rhesus babies she found six cases of deafness, "none of which had been suspected, although most of the children had been well cared for domestically and medically." She concludes that it "would seem, therefore, that the attention of otologists and pediatricians ought to be drawn to this possible sequel of Rhesus incompatibility . . . If every Rh negative woman is delivered where there are facilities for testing the cord blood and for an early exchange transfusion (repeated as necessary), then Rhesus children should cease to be crippled by kernicterus or deafness."

The neurological lesions of erythroblastosis fetalis in relation to nuclear deafness were described by Dublin in 1951 (see also his report of 1949). He examined the brains of seven newborn infants having erythroblastosis fetalis, particular attention being given to the auditory pathways. He

found cell injury in both the dorsal and ventral cochlear nuclei, the superior olivary nuclei, the medial geniculate body, the nuclei of the inferior quadrigeminal body. There were mild changes in the auditory cortex, but the cochlear nerves showed very little change. The auditory pathway, therefore, is widely and symmetrically involved. He stated that "the mechanism of cerebral injury in erythroblastosis fetalis is one of *anoxia*. The distribution of lesions is the same as that of any anoxic disorder, such as carbon monoxide poisoning . . . The cerebral anoxia of erythroblastosis results from the intravascular hemolysis, which deprives the capillaries, and the tissues they supply, of oxygen."

Kelemen (1956) points out that Gerrard (1952) was the first to submit the histopathological findings in the cochlea in his two cases of kernicterus which died during the neonatal period, and that no other such reports are available. He reports the third case of a three-day-old infant who died of erythroblastosis fetalis and describes the findings in the hearing organs, "displacement of the walls of the membranous labyrinth, symmetrically on both sides, was represented by dilatation of the vestibular scala, slight distension of the perilymphatic cisterna, and considerable dilatation of the endolymphatic sac with edematous rugae."

In connection with the three etiological factors thus far reviewed (heredity, rubella, and erythroblastosis) the fascinating article of Fisch (1955) "The Aetiology of Congenital Deafness and Audiometric Patterns," should be noted. He studied 250 cases of congenital deafness with reliable audiograms, and evaluated the pattern of audiogram as related to possible cause. Thus in deafness from maternal rubella, where the lesion is in the cochlea (developmental arrest of the organ of Corti as a whole), there is a flat audiogram. On the other hand, the most significant feature of deafness due to pathological conditions which complicate the circumstances of birth or immediate postnatal period (erythroblastosis, neonatal jaundice, anoxia) is "the selective loss of hearing for high frequencies" and a *sloping curve* with only moderate impairment of hearing (nuclear type of deafness). In these conditions the lesion is in the cochlear nuclei,

and principally the *dorsal* cochlear nucleus, which is the only part of the auditory pathway in which the fibers which carry high frequency impulses are concentrated. (He cites the interesting papers of Lewy and Kobrak, Gasser, Lorente de No, and others to prove his point.) Hereditary deafness (in contrast to the other two types) is associated with the "residual" type of audiogram (hearing only for loud low frequencies), because the organ of Corti is underdeveloped along the whole basilar membrane. "The 'residual graphs' represent those cases in which total deafness would exist as a result of severe lesions in the organ of Corti, but the vibratory, quasitactile component of hearing is preserved" (Bocca, 1952 and 1953). In 2000 cases studied he found "no cases with no remnants of hearing."

2. Causes During Labor and Birth.

That difficulties associated with the process of birth may be related to central nervous system damage and auditory disorders in young children has been pointed out by many authors, notably Myklebust, Windle, Doll, Moloy, and Strauss. Most of these studies do not analyze specifically the problem of nerve deafness, and much research in this specific field is needed. As Myklebust has stated: "A number of children with peripheral hearing impairment have no other etiology except that of presumed damage at birth. It is conceivable that research will reveal that birth damage can affect the blood supply to the inner ear, causing either deprivation or hemorrhage with resultant deterioration of the organ of Corti or other cochlear and auditory nerve functioning." Fisch has pointed out that the cochlear nuclei are possibly the most complicated and anoxia-sensitive basal nuclei of the brain.

Windle has demonstrated the major role played by anoxia in the causation of neurological disorders in the offspring. He points out that even brief periods of anoxia can produce profound and permanent changes, and he reminds us that Little, in 1862, drew attention to cerebral pathology in human infants as due to "abnormal parturition, difficult labors, premature birth, and asphyxia."

Myklebust indicates that central nervous system damage and auditory disorders at the time of birth have been related to prematurity, post-term delivery, prolonged labor, difficult labor, Caeserean delivery, breech and other atypical fetal presentations, the use of anesthetic drugs during labor and delivery, and especially asphyxia neonatorum.

In recent clinical reports on the etiology of infantile nerve deafness, Bordley ascribes 13 cases (out of 485) to birth injuries and five to toxemia of pregnancy; Fowler reports 21 cases due to causes during labor and four due to eclampsia in his series of 270 cases; and Kinney reports 24 cases (out of 630) as due to birth injuries.

3. Other Prenatal and Natal Causes—a. Ototoxic drugs.

The danger of transmission of ototoxic drugs from mother to fetus has been stressed by numerous authors. In 1848, Parak reported finding high concentrations of sodium salicylate in the urine of infants for several days, in cases in which this drug had been given to mothers 30 minutes before delivery.

Nicloux (1909) gave alcohol in milk to mothers one hour before delivery and found alcohol in the umbilical cord of the newborn in the same concentration as in the maternal blood. In 1913 Wade reported five cases of deaf-mutism attributed to chronic alcoholism in the mother. Taylor states that Pelley (1912) found "that the newborn baby of a mother who is addicted to morphine or opium is as much an addict as the mother, for the child's blood and tissues are as fully saturated with narcotic as hers."

Mosher (1938) and Taylor (1937) demonstrated the toxic effects on the organ of Corti of the offspring of quinine given to the mother.

The ototoxicity of drugs is the subject of a recent Wherry Memorial Lecture (1954) by Lurie. He points out that the ototoxic drugs—salicylates, quinine, ascaridole, neomycin and the streptomycin group—are all products of plant cell metabolism used in the treatment of bacterial disease, and are dangerous to the function of the ear. Woltz and Wiley have

demonstrated the transmission of streptomycin from the maternal to the fetal circulation.

Kinney listed four cases of deafness due to quinine given to the mother early in pregnancy, and Fowler reports one case due to overuse of drugs.

Almost 20 years ago Taylor emphasized that "if the otologist, in obtaining a history of each child showing a nerve deafness, will inquire carefully into the history of drugs administered to the mother during her term of pregnancy, the etiology of a number of perplexing and otherwise unexplained cases of nerve deafness may be solved."

b. Miscellaneous Intra-Uterine Causes.

1. That *virus diseases* (other than maternal rubella) and *serological incompatibilities* (other than Rh) may be etiological factors in deafness present at birth has been pointed out by authors already cited (Taylor, Aycock et al., Goodhill, Van Egmond).

2. Bordley (1952) emphasized that *maternal immunization* during pregnancy may cause deafness. He reported four cases attributed to the administration of immune globulin to mothers during the first trimester of pregnancy as prophylaxis against measles. He suggested that "some of the present work being done on prenatal immunization in some obstetrical and pediatric clinics should be assessed with the greatest care."

3. Congenital syphilis is no longer the significant cause of deafness it was formerly. Yearsley (1934) reported 187 cases in 4,314 deaf children in England (4.3 per cent), and Shambaugh (1928) reported 24 cases out of 1,192 in the United States (2 per cent). Ballenger (1947) indicated that the incidence of congenital syphilis among deaf-mutes has been variously estimated at from 3.5 to 25 per cent. In recent reports Bordley and Kinney list no cases of congenital syphilis and Fowler lists two cases (with interstitial keratitis).

4. Diabetes and *Cretinism* have been implicated as prenatal causes of infantile deafness. (Kelemen, Taylor, Yearsley, Hurwitz and Skipper). Kelemen (1955) submits the first

pathological report of the findings in the ear of a six months fetus delivered by hysterectomy of a diabetic mother.

5. Congenital atresia of the external auditory canal may produce deafness at birth, especially if there is malformation of the middle ear (Van Egmond). Altmann has written an excellent review of the subject (1951), and Wilson (1955) devotes a chapter to the subject of congenital abnormalities in his recent textbook "Diseases of the Ear, Nose, and Throat in Children."

C. Acquired Postnatal Causes.

According to Wilson (1955) severe deafness in infants and young children is usually caused by labyrinthitis or toxic damage.

In the pre-antibiotic era, meningitis (especially cerebrospinal meningitis) was the commonest cause of labyrinthitis. Thus Shambaugh in 1928, in reporting the cause of acquired deafness in children in schools for the deaf, lists meningitis as the leading cause of deafness in 1,192 cases studied. Meningitis accounted for 17.5 per cent as compared to scarlet fever (8.4 per cent), measles (8.2 per cent), influenza (7.1 per cent), pneumonia (4.5 per cent), pertussis (3.5 per cent), infantile paralysis (3.1 per cent), mumps (1 per cent), and suppurative otitis media and its complications (5.6 per cent). In Best's report for the same year, meningitis was the leading cause with 14.5 per cent as compared with scarlet fever (7.3 per cent), measles (5.7 per cent), pertussis (4.7 per cent), pneumonia (3.7 per cent), typhoid fever (1.9 per cent), infantile paralysis (1.9 per cent), diphtheria (1.4 per cent), influenza (.9 per cent), mumps (.8 per cent), disease of ear and mastoiditis (2.4 per cent).

In England, Yearsley reported in 1934 on a study of over 4,000 cases of "educational deafness" seen in 25 years. Of 2,935 cases of acquired deafness, meningitis was listed as the cause of 375 (13 per cent) as compared to measles (9 per cent), scarlet fever (9 per cent), influenza (.8 per cent), pneumonia (1.5 per cent), pertussis (2 per cent), diphtheria (2 per cent), mumps (0.2 per cent). Yearsley, however, lists

middle-ear suppuration and "middle-ear catarrh" as the cause in 1,424 cases (48.5 per cent).

In recent reports Bordley (1952) lists meningitis as the cause in 43, or 9 per cent, of cases out of 485 children with impaired hearing (from all causes—hereditary, prenatal, natal and postnatal). Meningitis in this listing is the leading determined cause. Of the other childhood diseases there were 31 cases of measles (Rubeola), 37 cases of unexplained fevers, eight cases of whooping cough, six cases of chicken pox, five cases of mumps, four cases of penumonia, two cases due to scarlet fever, and one case due to poliomyelitis.

Kinney (1953) reported on a study of 2,628 cases of impaired hearing in children. Of these, 940 were classified as perception cases and included 310 with unilateral loss (no hearing in one ear, normal hearing in the other) and 630 with partial (bilateral) loss. In the unilateral cases, "meningitis" is given as the cause in 23.9 per cent, measles in 23.2 per cent, and mumps in 10.6 per cent. In the 630 "partial loss perception cases" measles is blamed in 17.3 per cent as compared to meningitis 4.8 per cent, mumps 3.5 per cent, pertussis 2.7 per cent, "polio" 1 per cent. Kinney concludes that "the measles virus as a cause of perception hearing loss in children is probably of greater import than has been reported in previous publications."

Fowler and Basek (1954) reporting on postnatal causes of deafness in 189 children, lists ten cases due to meningitis, eight cases due to mumps, 14 cases due to measles and 45 cases due to otitis media. They point out that the high incidence of otitis media as compared to meningitis (4.5 to 1) in their cases is at great variance with the recent reports of Bordley and Scott-Moncrieff that meningitis is the commonest cause of postnatal deafness, but they cannot explain this difference.

Wilson points out that while scarlet fever may cause a diffuse labyrinthitis and meningitis, the most common cause of deafness in this condition is a labyrinthitis secondary to suppurative otitis media. Lindsay and Hemenway point out that this is also true in measles, and state that with proper

antibiotic treatment, this complication of bacterial otitis media should be a rare occurrence; therefore, since the advent of antibiotic therapy, the most frequent type of deafness caused by measles will be that due to the direct effect of the virus on the inner ear ("neuro-labyrinthitis," viral acoustic neuritis, measles meningo-encephalitis). They were able to find only three cases in the literature describing the pathology in the inner ear. They summarize the findings in these cases and give a detailed report of a fourth case showing "endolymphatic labyrinthitis" with secondary nerve degeneration.

That *drugs* used in the treatment of bacterial infections may cause nerve deafness has already been noted in the discussion of ototoxic drugs. In recent years, studies have been carried out on streptomycin, dihydrostreptomycin, and neomycin.

In 1952, Walker reported on a study of 93 cases of tuberculous otitis media (most of them in children), treated by streptomycin and dihydrostreptomycin. He found 68 cases with moderate to severe deafness. The deafness was often preceded by tinnitus and usually became apparent in the fifth or sixth month of therapy.

Dihydrostreptomycin is more likely to cause cochlear damage than streptomycin; however, both drugs have been found to cause deafness and vestibular disturbances. Lurie points out that there is definite degeneration of external hair cells and internal hair cells of the organ of Corti with secondary involvement of the ganglion cells of the cochlea. There is also degeneration of the hair cells in the crista of the semicircular canals and in the macula of the utricle. Neomycin affected the organ of Corti and not the vestibular apparatus. Lurie warns us that these drugs must be used with caution, for some patients will "pay the price of deafness with their use."

Trauma is listed as a cause of acquired deafness by numerous authors. Wilson states: "Trauma is a possible cause, but fracture of the skull likely to cause complete deafness would most probably prove fatal." Yearsley (1934), in reviewing 2,935 cases of acquired "educational" deafness lists

"injury" as a cause in 139 cases (4.7 per cent); and Shambaugh (1928) lists "skull fracture" as the cause in 2 per cent of his cases, and "fall" as the cause in 1 per cent. Trauma is also listed as a cause in the reports of Kinney, and in Fowler and Basek.

Schuknecht and his associates have reported interesting clinical and experimental studies of the relationship of head injury and deafness. In their most recent report (1956) they point out that "partial permanent deafness occurs in about 50 per cent of patients who incur a blow to the head severe enough to produce unconsciousness. Even a mild head blow without loss of consciousness can occasionally result in deafness." They classify deafness from blows to the head into three groups: *1.* Longitudinal fracture of the temporal bone usually causes conduction deafness through interference with the sound-conducting apparatus. There is often, in addition, a perceptive deafness for high frequencies due to trauma to the organ of Corti; *2.* Transverse fracture of the temporal bone passing through the labyrinth usually causes a profound loss of auditory and vestibular function; *3.* Labyrinthine concussion may cause perceptive deafness without roentgenological evidence of fracture. The significant pathological changes lie in the organ of Corti, with the severest damage in the upper basal turn.

THE PRESENT STUDY.

The records of 328 children referred to the Clinic for the Deaf Child of the Winthrop Foundation of the Massachusetts Eye and Ear Infirmary were studied to determine the probable etiologic factors. These cases include those seen at initial interview and subsequent visits to the Clinic by the author, as otologist in charge, during the years 1949 to 1952, and those first seen in prior years by other otologists of the Winthrop Foundation but re-evaluated by the author during follow-up interviews.

Most of the children had a complete diagnostic study consisting of: *1.* A detailed history and otological examination; *2.* estimate of hearing and speech capacity by a trained audiometrist; *3.* estimate of intelligence by a clinical psychol-

ogist; and *4.* interviews with parents or guardians by a trained psychiatric social worker. In selected cases, the study was supplemented by examination by a child psychiatrist, pediatrician, neurologist and other consulting specialists available to us at the clinics and laboratories of the Massachusetts General Hospital. In many instances, conferences with several or all of these specialists, including teachers and speech therapists, were held to aid in a total evaluation of the child and his physical, mental, emotional, social and educational needs. Wherever possible, with the aid of a full-time secretary and the social service worker, information was obtained from family, obstetrician, pediatrician, or referring medical or social agency.

TABLE I.

Age Distribution of 328 Deaf Children.
(At first visit to Winthrop Foundation).

Age (Years)	0-1	1	2	3	4	5	6	7	8	9	10
Number of Children	2	16	85	60	61	49	23	20	8	3	1

The most significant information relating to the probable cause of hearing loss was obtained from a detailed history similar to that suggested by Myklebust. It included:

1. Family history of deafness, speech problems and neurological disorders in parents, siblings, and other blood relations.

2. Prenatal, natal, and neonatal history.

3. History of illnesses, injuries, and inoculations since birth.

4. Neuromuscular, genetic development of the child.

5. Hearing and language development of the child, and

6. Educational history to date.

As will be noted, however, in Table II, we were unable to obtain sufficient data from the information available to determine with any certainty the probable cause of deafness in 148 of these children (45 per cent). This may be explained in part by the fact that some of our children were adopted,

or were referred from rural communities, and the pertinent information such as details of birth, neonatal history, and studies of serology and Rh factors were not available to us.

In Table I is shown the age range of the 328 children when first referred to the Winthrop Foundation. The age factor is related to etiology in that the younger the child, when the

TABLE II.

Causes of Severe Hearing Loss in the Children Studied at the Winthrop Foundation.

Cause	Number	Percentage
A. Hereditary (Familial)	15	4.6
B. Acquired Prenatal and Natal Causes (116 or 35%)		
1. Maternal Rubella	36	11.0
2. Rh Incompatibility	23	7.0
3. Causes During Labor and Birth		
a. Prematurity, Twins, Placenta Praevia, Toxemia	18	5.5
b. Traumatic labor, Brain injury, Cerebral palsy	29	9.0
c. Cyanosis, Icterus	3	1.0
4. Congenital Anatomical Defects	7	2.0
C. Acquired Postnatal Causes (49 or 15%)		
1. Meningitis	17	5.2
2. High fevers, Pneumonia, etc.	11	3.3
3. Measles	6	2.0
4. Mumps	2	0.6
5. Pertussis	1	0.3
6. Rabies Vaccine	1	0.3
7. Skull Injuries	4	1.2
8. Middle Ear Disease	7	2.0
D. Cause Undetermined	148	45.0
Total	328	100.0

deafness was first recognized and competent help sought, the more likelihood there was of finding alert and intelligent parents, and of obtaining pertinent etiologic data. Some of these children were born before the significant relation of maternal rubella and Rh incompatibility to deafness was generally known, and this valuable information was not obtainable from the parents or their physicians.

Less than one-third of the children (103) were examined before the age of three, and only about half before the end of the fourth year, despite the teachings of most workers in this

field that any child "who has not developed speech by the age of two, warrants very careful investigation of his hearing." (Bordley and Hardy. See also Wishart, McFarlan, Lurie, Fowler, Kinney.)

The estimate of intelligence of these children may shed some light on the etiological factors, as it certainly does on

TABLE III.

Intelligence Quotient of 202 Deaf Children Tested at Winthrop Foundation.

Cause of Hearing Loss	Number Tested	Normal No.	Normal %	Retarded No.	Retarded %	Superior No.	Superior %
A. Hereditary (Familial)	6	4	66.6	1	16.6	1	16.6
B. Aquired Prenatal and Natal:							
1. Maternal Rubella	26	18	70.0	3	11.0	5	19.0
2. Rh Incompatibility	17	12	70.6	3	17.6	2	11.6
3. Causes during labor and birth:							
a. Prematurity, Twins, Placenta previa; Toxemia	12	7	58.3	4	33.3	1	8.3
b. Traumatic labor, Brain Injury, Cerebral Palsy	19	10	52.6	9	47.4	..	.....
c. Cyanosis, Icterus	3	2	66.6	1	33.4	..	.....
4. Congenital Anatomical Defects	5	4	80.0	1	20.0	..	.....
C. Acquired Postnatal Causes:							
1. Meningitis	11	8	73.0	2	18.0	1	9.0
2. Fevers	7	5	71.0	..	.....	2	29.0
3. Measles	5	5	100.0	..	.....	..	.....
4. Mumps	1	1	100.0	..	.....	..	.....
5. Pertussis	1	1	100.0	..	.....	..	.....
6. Rabies Vaccine	1	..	.....	..	.....	1	100.0
7. Skull Injuries	2	1	50.0	..	.....	1	50.0
8. Middle Ear Disease	6	6	100.0	..	.....	..	.....
D. Cause Undetermined	80	64	80.0	8	10.0	8	10.0
Total	202	148	73.0	32	16.0	22	11.0

their educational potential. Sufficient data was present in the records of 202 of these children to enable us to classify them according to their I.Q. as normal, superior, or retarded. This classification was based, not only on the results of several non-verbal intelligence tests repeated at intervals, but also on reports of educational progress and behavior, made by teachers, parents, social worker, and psychiatrist. The difficulties and techniques of examining the mental capacity of young children with auditory disorders have been stressed by numer-

ous authors (Ewing, Doll, Gesell, Gerver, Goldstein, Hardy, Myklebust, Utley). Table III summarizes the recorded observations on the I.Q. of 202 children grouped by the etiological classification shown in Table II.

REPORT OF FINDINGS.

The essential findings in this study are sumarized in Tables I, II, and III. More detailed report on the various etiologial factors follows:

A. Hereditary Deafness.

In this group there were 15 children, or 4.6 per cent of the total number studied. Included in this category were children deaf apparently from birth or infancy, whose history revealed at least one sibling with hearing loss in early childhood and/or at least two successive generations in his direct line of descent, with a history of deafness from birth or early life, as suggested by Bordley and Hardy (1951), and no other ascertainable cause. The age at first visit ranged from one to ten years, with an average of three plus years. The I.Q. was known in six of these children, four labeled normal, one retarded, and one superior. It is of interest that the child with superior intelligence, first seen at age five years, had a hearing loss of 95 db. at frequency 512 cycles per second, and gave no response at the higher speech frequencies at maximum intensity of the audiometer. The child with mental retardation was first seen at age ten years, and showed a hearing loss of 70, 75, and 80 db. in the "vital" speech frequencies (500-2000 cycles per second, inclusive) in the better ear.

B. Acquired Prenatal and Natal Causes.

1. Maternal Rubella.

This group comprised 36 cases with a definite history of maternal rubella early in pregnancy. The age range was one to 9.5 years and averaged five plus years at first visit. The I.Q. was known in 26 children, 18 considered normal; five superior; and three retarded. Four of these children also had congenital cataracts; two had congenital heart lesions;

and two were born prematurely and required a prolonged period of incubation.

2. Rh Incompatibility.

In this group were included only those cases with a definite history of Rh incompatibility or kernicterus. Most of them were referred to us by hematologists or pediatricians for audiological work-up, the Rh incompatibility having been established by them prior to referral to us. There were 23 children ranging in age from one to 7.5 years (average age 4.5 years). The I.Q. was reported in 17 cases: 12 normal, two superior, and three retarded. Three of these children were born prematurely (two of them had cerebral palsy, and one had a sister who was born blind). Six of the children in this group had cerebral palsy, and one was epileptic. The three children classified as retarded fell into this latter group.

3. Causes During Labor and Birth.

a. Prematurity, twin births, placenta previa, toxemia of pregnancy. In this group are classified 18 cases with an age range of one to eight years (average four years). All of them have a history of premature births requiring incubation and oxygen postnatally. Three of these were also twins, two were placenta previa cases, and four cases gave a history of toxemia during pregnancy. The I.Q. in 12 of these was known: seven normal, one superior, and four retarded.

b. Traumatic labor, (Brain injury, cerebral palsy). This group, the second largest with known etiology in this study, contained 29 cases in which the cause of hearing loss was ascribed to the trauma of difficult prolonged labor, with the life of the child or mother greatly endangered. Their age, at first visit to the Winthrop Foundation, ranged from one-and-one-half to seven years and averaged four years. Fifteen of these showed difinite evidence of brain injury: cerebral palsy, convulsions in neonatal life, monoplegia, limb injuries, prolonged cyanosis, etc. Several of them required prolonged resuscitation. Four were difficult breech deliveries. One case, a face presentation, had malformation of the cervical and dorsal vertebrae (Weil syndrome). In two cases, the mother died during labor. One child was a transverse pres-

entation and weighed 11 lbs at birth. In two cases the mother hemorrhaged and was transfused repeatedly during labor, and the children were cyanotic and required oxygen for three and seven days respectively. One case was a breech delivery who suffered from neck and foot injuries and was considered to have mongolism. The I.Q. was reported in 19 of these cases: ten were classified as normal and nine retarded, (none superior).

c. Cyanosis and Jaundice. In this group are included three children, aged four, six, and seven years at first visit. The four-year-old was cyanotic for several days after birth. His intelligence is recorded as normal. He was profoundly deaf. The second child had delayed respiration for 45 minutes, had an I.Q. of "low normal," and had hearing loss averaging 60 db. in the speech range in the better ear. The third child, labeled "retarded," had severe jaundice and convulsions early in life, and showed a hearing loss of 50-60 db. in the better ear.

4. Congenital Anatomical Defects.

This group included seven cases. They differed from the other groups in having milder hearing losses. Four of these children had microtia; three had cleft palate (one of them with microtia and mongolism), and one had cleft palate and harelip. Five of these children had conduction deafness (average 50 db. in speech range). One child had microtia and profound deafness (90-100 db. loss) in one ear, with the other ear normal. The average age at first visit was four (range 2-7 years). Five I.Q.'s were reported: four normal, one retarded.

C. Acquired Postnatal Causes.

In this category are included 49 children (15 per cent of the total) who were referred to the Clinic for the Deaf Child because of hearing and/or speech difficulties, and who appeared to have had normal hearing and speech development until the intervention of an acute lliness or injury.

1. Meningitis and/or Encephalitis. In this group are included 17 cases with a definite history of meningitis and/or

encephalitis with subsequent hearing loss. Four of these had known meningococcal meningitis, three had pneumococcal meningitis, one had tuberculous meningitis and one had influenzal meningitis. The other cases had been diagnosed as "meningitis" by the referring physician, but the organism is unknown. Two of the children had associated paralysis; one had temporary hydrocephalus. Most of them were profoundly deaf. They ranged in age from two-and-a-half to six years (average four-and-a-half years). The I.Q. is reported in 11 cases: normal in eight, retarded in two, and superior in one. The one "superior" child, a case of influenzal meningitis, was six years old when tested, and had a mental age of ten years. He was profoundly deaf (75, 85, and 90 db. loss in the vital speech frequencies in the better ear).

2. Acute Febrile Disease. Eleven cases. Age range one to seven years, average three-and-a-half years. I.Q. reported in seven cases: five normal, none retarded, two superior. Four had pneumonia, two had severe "virus" infection, and the others had an acute febrile disease of undetermined etiology.

3. Rubeola. Six cases; age range two to six years, average four years. I.Q. reported in five—all normal. Two of these children had only unilateral nerve deafness, and one had a bilateral mild nerve deafness, two had partial deafness (average 70 db. loss in speech range), one had profound deafness.

4. Parotitis. There were only two cases of deafness following mumps, (ages four and six years) one averaging 55 db. loss and the other 90 db. in speech range.

5. Pertussis. One case, aged three, normal intelligence, with mild nerve deafness (20-30 db. in speech range).

6. Rabies Vaccine. There was one child, of superior intelligence when first tested at age of five years, whose profound deafness followed 21 "Pasteur treatments" at the age of two years.

7. Skull Injuries. Head trauma was the cause of hearing loss in four children. One child, first studied at age nine, had superior intelligence, and a hearing loss averaging 80 db. in the speech range as a result of bilateral fracture through

the petrous pyramids. One four-year-old gave a history of "skull fracture" in infancy, and showed a hearing loss of 40 to 70 db. in the speech range; however, in this case there was also a history of difficult labor. The other two children, aged two-and-a-half and three years when first seen, gave a history of head injury at age two, with subsequent unsteady gait, and showed "absent caloric tests" and profound deafness.

8. Middle Ear Disease. This category includes seven children with otitis media and moderate deafness who presented special problems of rehabilitation and, therefore, were not treated in the regular outpatient clinic, but were referred to the Winthrop Foundation for follow-up. In two of these, the diagnosis of possible otosclerosis was made and they will be followed at the Winthrop Foundation. The I.Q. in six of these was determined—all normal.

D. Cause Undetermined.

Unfortunately in the largest group of these children, 148 or 45 per cent of the total studied, we were unable to determine the cause for reasons partly explained above. They ranged in age at the first visit from one to ten years, with an average of four years. The I.Q. was reported in 80 of these children—64 normal, eight superior, and eight retarded.

COMMENTS AND DISCUSSION.

Several findings in this study deserve comment. The first is the age when competent otological help was sought. It is unfortunate that less than one-third of these children were examined before the age of three, and only about 50 per cent before the end of the fourth year. This bears out the statements of Wishart that "the ignorance regarding the importance of hearing in a child under two years of age is appalling . . . The majority of congenitally deaf children come to the clinic too late and go to preschool training class without any training in lip-reading and with voices that are dull, flat and lifeless. This occurs because two essentials in their training have been missed. It has not been started early enough nor has it been done by the potential teacher every baby has, its mother." He advises that "the mother should start the train-

ing as soon as the defect is suspected, perhaps at six months of age, and that special education should be started, if possible, at the age of two, and certainly at the age of three. If these early critical years are lost the child's opporunity to acquire fluent speech is lost forever." Otologists must teach every doctor, and especially the pediatrician, that it is of the utmost importance to detect deafness and to start training as early in life as possible (Ewing), and that this can be done in the first year of life (Whetnall, Richmond et al.).

McFarlan, in discussing Wishart's excellent paper, points out that in the handling of the deaf child "the two greatest mistakes are to say, 'wait until the child grows up,' and worse still, to diagnose a 'mental retardation'." This study bears out the findings of numerous observers that the intelligence of the deaf child is comparable to the normal hearing child (Gesell, Gerver, Hardy, Heider, Lassman, Myklebust, Pinter, Strauss, Streng et al.). Seventy-three per cent of the 202 children whose I.Q. was reported in this study showed normal intelligence, 16 per cent were "retarded," and 11 per cent were "superior." The greatest incidence of retardation was found in the children injured during the birth process, and this tragic complication is preventable.

The etiologic diagnosis of deafness in a young child is often difficult even after a careful history and otologic examination because of the absence of pertinent information. The rapidly accumulating knowledge of the numerous potential causes of infantile deafness, especially during the prenatal, natal and neonatal period, has not been adequately disseminated among the medical profession and others concerned with the welfare of children. Otologists have a continuing duty to disseminate this knowledge, and in the words of Dr. Fowler, Sr., to "preach the gospel of early detection" to all concerned.

The large percentage of cases of undetermined cause (45 per cent in this study) has been mentioned. Kinney (1953) analyzed 630 "partial perception cases," and was unable to determine the cause in 43.3 per cent. Bordley's "Analysis of etiologic factors underlying impaired hearing of 485 children" (1952) showed 140 cases of undetermined cause (30 per cent).

Table IV shows comparative etiologic data of several recent reports. Under the heading "Labor and birth" are included cases of deafness ascribed to toxemia, prematurity, and birth injuries.

The variations in the incidence of the causes of infantile deafness is often striking. An etiologic diagnosis can seldom be made with any degree of certainty since, as Fowler has pointed out, "the reasoning used to classify the groups is *'post hoc propter hoc'* reasoning." Some of the reports cover only cases studied in schools for the deaf (Best), others in

TABLE IV.

Etiologic Data Compiled from Recent Reports.
(Per cent of number reported).

CAUSE	Unknown	Heredity	Maternal Rubella	Rh Incompatibility	Labor and Birth	Meningitis	Measles
Present Study	45	4.6	11.0	7.0	14.5	5.2	2.0
Bordley (1952)	30	4.0	5.0	6.0	4.0	9.0	6.0
Goodhill (1950)	....	....	20.0	3.0	....	10.3	....
Fowler and Basek (1954)	....	3.7	4.5	4.5	9.0	4.0	5.0
Kinney (1953)	43.3	14.6	....	2.2	3.8	4.8	17.3

otological centers (Bordley). Some include mainly severe nerve deaf cases (as in this study); others include milder cases of mixed deafness or conduction deafness. Statistical comparisons are, therefore, inaccurate and may be misleading; however, it is becoming clear that, with our newer knowledge of the potential *in utero* causes, heredity as a cause has been greatly exaggerated in past reports. Too many cases have been loosely labeled "congenital" or hereditary.

In this study, as in other recent reports (Bordley, Kinney), there was not one case caused by syphilis.

We were impressed with the high incidence of deafness ascribed to the difficulty of labor and birth in our series. Certainly most of these cases can and should be prevented.

Perhaps, here lies the major urgent indication for dissemination of knowledge regarding the etiology of infantile deafness among all physicians and the interested laity. Much public health work can be done to prevent the scourge of infantile deafness from erythroblastosis, German measles, the trauma of labor and delivery and from most of the acquired postnatal causes. Next to prevention, the most pressing need is early detection of deafness (during the first year of life) and the initiation of rehabilitation in the first years of life.

SUMMARY AND CONCLUSIONS.

The records of 328 deaf children studied at the Winthrop Foundation of the Massachusetts Eye and Ear Infirmary are analyzed as to etiological factors.

The causes of deafness, the age at first visit, and the I.Q. of 202 of these children are reported.

The difficulties in making a precise etiologic diagnosis are pointed out. The large number of cases with "cause undetermined," is discussed and partly explained.

The study points out that the intelligence of deaf children as a group is comparable to normal hearing children.

The importance of early detection of infantile deafness and the need for early training is stressed.

The duty of otologists to disseminate widely the recently acquired knowledge as to the etiology of deafness in early childhood is emphasized, and the possibilities of prevention of most of the causes of infantile deafness are noted.

The pertinent literature is reviewed and a bibliography is appended.

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EUSTACHIAN TUBE FOREIGN BODY.

Report of a Case.*

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Reports of foreign bodies retained in the Eustachian tube have been rare since bouginage and electrolytic treatments of the tube have lost favor. Broken bougies remaining as foreign bodies in the Eustachian tubes have been reported by Wendt (1869),[3] Andry and Reynolds (1880),[3] Harris (1901),[4] Tansley (1902),[11] Duel (1903),[2] Philips (1905),[8] Simpson (1905),[9] Stimson (1915),[10] Hastings (1937),[5] and Mangiarcina (1940).[6] The bougie tip had remained in the Eustachian tube of Hasting's patient for 20 years. In the discussion of a paper by Harris in 1904, Dench[1] reported having seen three gold bougie tips removed from a single ear at one time.

In a review of the literature written in 1920, Guthrie collected the following unusual foreign bodies of the Eustachian tube:[3]

1. A grain of rice reported by Urbanschitsch in 1878.
2. A sewing needle reported by Schwartze in 1885.
3. A straw reported by Camerer in 1897.
4. A cherry stone reported by Trautman in 1898.
5. A stalk of grass reported by Piffli in 1907.

This case is similar to one reported by McNaught in 1948, in which a piece of slag lodged in the Eustachian tube after having been washed through a perforation in the tympanic membrane.[7]

A 24-year-old welder was seen in September, 1956, because of severe pain and drainage in the right ear since swimming two weeks before. The history revealed that a piece of slag had lodged in his right ear canal

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while he was welding three months previously. The slag was removed by irrigation of the ear canal in a doctor's office. This was very painful to the patient, and was followed by discharge and severe pain. Under antibiotic therapy the pain gradually subsided, and the discharge stopped. Considerable hearing loss had been present since the original injury.

Physical examination revealed copious pulsating purulent discharge in the right ear canal issuing from an anterior-inferior marginal perforation of the drum. Marked tenderness was present over the mastoid process. The nasal septum was deviated to the right, and the nasal mucosa was diffusely inflamed with mucopurulent post-nasal discharge. The examination was otherwise within normal limits. The clinical diagnosis of acute

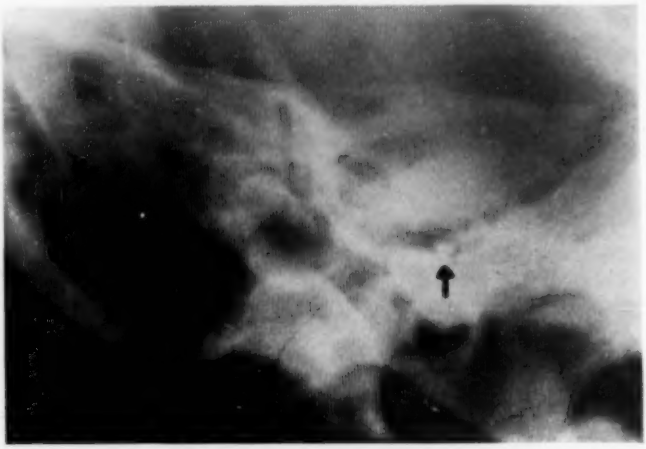

Fig. 1. Stenvers' Position. The arrows indicate the metallic foreign body lodged at the isthmus of the Eustachian tube.

otitis media and mastoiditis was confirmed by radiographs. The films also revealed a metallic foreign body lodged at the isthmus of the right Eustachian tube (see Figs. 1, 2).

Treatment was instituted with antibiotics. The pain and discharge rapidly subsided. When the ear was dry, audiometry revealed a normal bone curve and an average of 40 decibel loss for the speech frequencies by air conduction.

An attempt to dislodge the foreign body by direct inflation was unsuccessful. Considerable force was necessary to dislodge it with an Eustachian tube bougie. The fragment was then blown into the tympanic cavity by direct inflation, and was removed with a suction tip through the perforation of the tympanic membrane. The ear remained dry, but attempts to close the perforation by cautery of its edges and patching proved futile. A myringoplasty was recommended. The insurance company referred the patient to another otolaryngologist who concurred in this recommendation.

The patient again consulted the physician who had originally removed the slag from his ear canal. This doctor recommended against surgical closure of the drum, and myringoplasty was subsequently refused by the patient.

Interestingly enough, the patient has since been treated elsewhere for a slag burn of the left external canal and tympanic membrane. This perforation closed spontaneously.

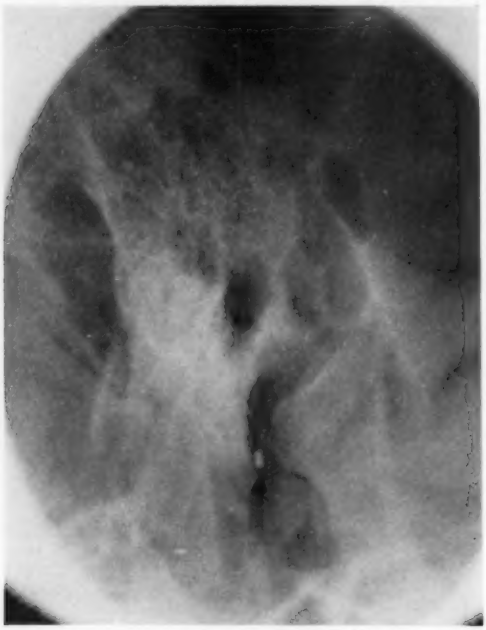

Fig. 2. Mayer's Position. The arrows indicate the metallic foreign body lodged at the isthmus of the Eustachian tube.

CONCLUSIONS.

1. Since slag lodged in the external canal is frequently associated with perforation of the tympanic membrane, irrigation of the ear canal for the removal of the foreign body is definitely contraindicated. In addition to the danger of introducing infection there is the additional hazard of washing small fragments of the foreign material into the tympanic cavity and Eustachian tube.

2. In spite of the infrequency of reports in the literature, when slag burns of the tympanic membrane are accompanied by prolonged infection, or when surgical closure of the perforation is contemplated, radiographs should be taken to search for foreign bodies located within the osseous portion of the Eustachian tube.

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CLOSED CERVICAL TRACHEAL FRACTURE: A CASE REPORT.

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Closed tracheal injuries are not frequently reported in surgical literature. The management of tracheal lacerations are well covered in recent reports. A number of authors give detailed reviews of surgical repairs, either by primary anastomosis, or with various prostheses bridging tracheal defects in lacerating or avulsive trauma.

The following authors[1,2,3] have laid down the basic steps in the care of tracheal injuries and also give a review of complications and management.

The following case of tracheal fracture, resulting from a closed injury, was managed "conservatively," with an excellent clinical response and without posttraumatic sequelae.

This case is reported for interest, and should not deter from other methods of care in these injuries.

For review purposes, this injury is caused by compression or impact of the trachea in a closed space. The cartilaginous membrane is usually torn, with or without fracture of the tracheal rings themselves.[4]

This report is of an interesting case of closed tracheal fracture, treated without surgical intervention.

The patient, a 24-year-old white woman, was admitted to a local hospital, (San Antonio, Tex.), on October 25, 1955, following an automobile accident. She sustained a chin laceration, contusion of the neck, and shortly after admission developed cervical subcutaneous emphysema.

Physical examination revealed a blood pressure 130/72, pulse 86 regular, respiration 24, no cyanosis. The patient was not in shock. Positive findings were of a chin laceration, contusion of left anterior-lateral neck, middle third, and crepitus of the soft tissues anterior to the trachea and bordering laterally by the borders of the sternomastoid. The crepitus extended superior to the hyoid bone and inferiorly into the suprasternal notch. There were no other objective or subjective findings.

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Laboratory data: Hemoglobin 15.1, white blood cells 13,120, polys 76, lymph 16, stabs 2, monocytes 1; urinanalysis, specific gravity 1,014, alkaline reaction, negative, sugar and albumin.

Hospital course: Patient placed on penicillin 800,000 units twice daily, and streptomycin 1.0 gm. daily. Roentgenogram of thorax and cervical area revealed clear lung fields and cervical subcutaneous emphysema in the anterior and middle compartments of the neck.

October 29, 1955, the patient's hoarseness was disappearing, cervical emphysema decreasing, and she was afebrile. On November 5, 1955, the hoarseness was improved; the cervical emphysema was almost absent. Lung fields were clear on fluoroscopy, and the vocal cords moved on respiration and appeared intact. Antibiotics were discontinued, and patient was discharged from the hospital.

She was seen in the office on November 26, 1955. Indirect laryngoscopy revealed intact cords, no edema. Fluoroscopy revealed clear lung fields and movable vocal cords on phonation. She noted that she occasionally had episodes of hoarseness which lasted one or two hours, and then gradually subsided.

The patient was last seen on January 5, 1956, the voice completely normal, no induration in the neck and clear lung fields on fluoroscopy examination.

CONCLUSION.

This case is reported as a matter of interest. The closed tracheal fracture was treated without surgical intervention, and with a satisfactory clinical response.

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PHENYLBUTAZONE AS AN ADJUNCT IN THE TREATMENT OF ACUTE OTITIS EXTERNA AND OTHER EDEMA OF THE EAR, NOSE AND THROAT.

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Edema associated with allergy and angioneurotic edema specifically is not considered in this paper. Depending upon the etiology, traumatic or infectious edema is usually managed with both local and general measures. These involve the use of hot or cold applications locally, wicks, compresses, drops, ointments and the various antimicrobials; generally, the relief of pain and oral or parenteral antibiotics. The past few years have witnessed the advent of the usual anti-inflammatory agents such as the proteolytic enzymes in local, oral and intramuscular forms, and the various modifications of the Cortisones.

This discussion limits the pathologic states described to the edema associated with acute external otitis, either primary, or secondary to a primary otitis media, furunculosis of the nose, after nasal operations such as rhinoplasty and septectomy and acute thyroiditis (see chart). Even with careful technique and minimal trauma when cleaning the external auditory canal, for example, and using a judicious combination of the above named agents, the average time for subsidence of edema was six to nine days, occasionally lasting as long as three weeks in several stubborn cases of external otitis secondary to otitis media; however, using the same agents as indicated, but without enzymes or hormones, and with Butazolidin,® the edema in external otitis, for example, subsided in 48 to 72 hours, and in practically all cases in which it was used within four or five days at the most. As can be seen in the chart, edema either did not develop at all or lasted only a few hours in the nasal cases; without Butazolidin® and

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using other anti-inflammatory agents, swelling required an average of five to seven days to subside. With phenlybutazone the edema of the painful and completely shut canal was controlled so rapidly that usually by the second office visit, two days after onset of treatment, the lumen was large enough to allow a more thorough cleaning of the depths, thus, facilitating resolution of the infection.

With the use of the proteolytic enzymes disadvantages may be noted: vagaries in buccal or sublingual absorption, pain

CHART.

Type of Case	No. of Cases, Routine Treatment, Including Enzymes and Hormones	Average Duration of Edema	No. of Cases, New, Using Butazolidin®	Average Duration of Edema
1. Acute Primary External Otitis	28	6-9 days	59	3-5 days
2. Acute External Otitis Secondary to Acute Otitis Media	5	1-3 wks.	5*	3-4 days
3. Nasal Furunculosis	7	5-7 days	6	2-3 days
4. Rhinoplasty	3	4-5 days	2	24 hrs.
5. Septectomy	5	6-7 days	3	12-18 hrs.
6. Acute Thyroiditis	3	1-3 wks.	2	2-3 days

*These five are the same, first treated routinely and then finally with phenylbutazone.

at the site of injection, and tendency to serious allergic reactions.[1] The first two are particularly noted in children. The expense of hormones and tendency toward temporary increase of edema with these hormonal products, is also to be considered. On the other hand, these disadvantages are minimized, and more accurate dosage obtainable with the oral route is important.

Butazolidin® for adults is begun with either the 100 mgm. tablet or the Alka capsule form after first obtaining a negative history of peptic ulceration, anemia or allergy.[2] A total of 600 to 800 mgm. is given the first day on a full stomach, with a decrease to 400 mgm. for the next two days. Should the individual case require it, the last dosage may be continued for another three days. The dosage for children is proportionately smaller. The salt intake should be restricted. This short duration of treatment also tends to decrease the frequency of side effects.

In the group of cases under discussion the only reactions noted were gastric upsets in two patients. These improved when the Alka capsule was substituted. There were five cases of particular interest to the otologist: these were cases of acute otitis media submitted to myringotomy and subsiding with appropriate treatment after culturing and sensitivity testing for the most effective anti-microbial. After a period of time varying from five days to three weeks, the discharge from the middle ear was the immediate exciting cause of a fulminating external otitis obscuring the healing drum membrane. In all five cases Butazolidin® effected a rapid subsidence of canal inflammation and edema, and the drum was found intact after treatment.

Only two of the more interesting ear cases will be mentioned briefly here: one finally remembered a history of external otitis treated nine months previously without sequellae and dry until after myringotomy, the middle ear discharge apparently lighting up a dormant canal infection. The second case involved a diabetic in whom the middle ear discharge and canal infection did not subside for three weeks after onset of intensive specific treatment, and in desperation phenylbutazone was used in the above mentioned doses with the result that complete healing of the drum and subsidence of the external canal infection occurred in three days while still using the original antibiotic. Two patients in whom the clinical diagnosis of acute thyroiditis was made by finding a slight to moderate swelling of one or both lobes of the thyroid gland associated with exquisite tenderness of the involved areas very rapidly cleared of symptoms under Butazolidin® and refused to undergo further diagnostic tests. An interesting finding in two patients not sought for, with relief of edema in mind, was a complete disappearance of facial acne. This could be attributed to the anti-inflammatory action of the phenylbutazone and suggests further investigation. One patient stated that even the pores of the skin about the nose and forehead were much smaller.

SUMMARY.

1. Drug for drug, phenylbutazone is the most potent and

effective anti-inflammatory agent with non-hormonal advantages yet offered for edema, traumatic or infectious, of the ear, nose and throat. It does not disrupt endocrine function, and it is not dependent upon it.

2. Used with precaution and due regard for anemia, allergy and peptic ulcer tendency it is safe and without side effects.

3. By rapid absorption of edema in diffuse external otitis cleaning and more effective treatment can be accomplished within two or three days.

4. In stubborn cases of external otitis associated with otitis media that do not resolve readily by the usual methods, phenylbutazone was found to stop completely the drainage from the middle ear while still using the original antibiotic, and facilitate canal resolution within three to five days after starting therapy.

5. The mechanism of action is as yet not elucidated, but its effectiveness is so rapid that further study is warranted with a view to extending its field of action and application, particularly to other head and neck edema, including laryngeal inflammation.

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124 West Princeton Avenue.

TRANSMISSION LOSS ACROSS THE SKULL IN A PATIENT WITH KNOWN TOTAL MONAURAL DEAFNESS.†‡

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SURVEY OF THE LITERATURE.

Several writers have reported their findings on the transmission loss across the skull which occurs for air conducted sounds. These reports are of importance clinically because they are used in determining under what conditions a masking noise should be presented to the non-investigated ear for pure tone air conduction measurement.

Fowler[1] found that at 45 db. or more over the normal threshold the opposite ear receives speech sounds by cross-audition. Fowler[2] states in another reference that an air conduction masking sound above 35-50 db., depending on frequency, is sufficiently intense to be sensed by the contralateral ear (at its threshold or above) if the bone conduction in this contralateral ear is not sufficiently depressed to prevent it. Hughson and Westlake[3] state that cross-hearing is likely to occur if an individual has a difference between the two ears of 30 db. or more. Sparrevohn[4] breaks down the transmission loss at individual frequencies: 21 db. at 128 cycles, 23 db. at 256 cycles, 19 db. at 512 cycles, 34 db. at 1024 cycles, and 34 db. at 2048 cycles. Saltzman[5] suggests that 50 db. represents the loss for air conducted sounds through the head uniformly at all frequencies. Tschiassny[6] reports an attenuation increasing with frequency averaging 55-75 db. in two monaurally deaf patients. If the healthy ears were kept closed, the loss decreased to the level of 35 to 60 db. Weille

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‡Based on research conducted at the Audiology and Speech Center, Walter Reed Army Medical Center, Washington, D. C.

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and Gargano[7] claim that about 50 db. are required for sound to go around the head to the opposite ear if it is covered by a well-fitting earphone, but do not specify the transmission loss for specific frequencies.

The difference in findings by the investigators quoted on the degree of transmission loss across the skull may be due to one of the following factors: *1.* Inter-individual variations in the impedance of different skulls; *2.* differences in the degree of deafness present in the supposedly deaf ear in the

TABLE I.

Transmission Loss Across Skull in a Patient with Total Monaural Deafness.

	Right Ear	Left Ear
Frequency	Point at which Response was Elicited in Normal Ear	Hearing in Better Ear
125 cycles	45	0
250 cycles	45	−5
500 cycles	55	0
1,000 cycles	65	0
2,000 cycles	65	25
4,000 cycles	60	20
8,000 cycles	80+	50

subjects used and possible slight differences in the hearing of the non-investigated ear; and *3.* the sound isolation provided by the different earphones used.

REPORT OF CASE WITH TOTAL MONAURAL DEAFNESS.

The patient is a 24-year-old private first class, in the Army, on the neuro-surgical ward of the main section of the hospital, who was referred to the investigator by the Chief of the Ear, Nose, and Throat Section. He had known total deafness in the right ear, resulting from an automobile accident in which both the acoustic and vestibular branches of the VIIIth cranial nerve were totally destroyed on the affected side. Vision and vestibular responses were completely absent on this side. The patient reported a constant tinnitus in his right ear. The otologist in charge* was of the opinion that the presence of tinnitus could be explained on the same basis as the tinnitus which is sometimes present when the VIIIth nerve is severed surgically.[8] Pure tones were introduced through an earphone over the patient's deaf ear in the orthodox manner, and the point at which the normal ear picked up these sounds was recorded for each frequency. These readings give us an idea of the transmission loss across the skull for air-conducted sounds in this patient. The results are shown in Table I.

*James P. Albrite, M.D., Director, Audiology and Speech Center, Walter Reed Army Medical Center, Washington, D. C.

The results of testing 8,000 cycles by air conduction showed no response at the maximum level of the audiometer. At this frequency, however, a loss of 50 db. was present in the better ear. A slight loss was present at 2,000 cycles and 4,000 cycles, and the transmission loss across the skull is the figure shown minus the degree of loss in the better ear, *i.e.*, 2,000 cycles: 65 minus 25 db. equals 40 db. and 4,000 cycles: 60 minus 20 db. equals 40 db. This gives us an average transmission loss of 53 db. for the three mid-frequencies.

SUMMARY.

The literature on the transmission loss across the skull which occurs for air-conducted sounds is reviewed. A case of known total monaural deafness is reported. The attenuation loss across the skull for air-conducted sound, determined by testing the impaired ear without masking, is shown. The attenuation loss for air-conducted sound varies at different frequencies. The amount of masking used for air-conduction measurements should be varied according to the frequency tested.

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6. Tschiassny, K.: The Mechanism of Shadow Hearing. *Arch. Otolaryngol.*, 55:22-30, 1952.

7. Weille, F. L., and Gargano, S.: Facts and Fallacies of Bone Conduction. The Laryngoscope, 63:182-211, Mar., 1953.

8. Dandy, W. E.: Ménière's Disease Systems, Objective Findings in Treatment in Forty-Two Cases. *Arch. Otolaryngol.*, 20:22, July, 1954.

PROGRAM FOR THE SCIENTIFIC SESSION OF THE THE AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

March 10, 11, 12, 1959

"Neck Dissection: A Clinico-Anatomical Study of 200 Cases."
George F .Reed, M.D., Boston, Mass.

"Evaluation of Laryngectomy with Radical Neck Dissection."
John J. O'Keefe, M.D., Philadelphia, Pa.
Open Discussion.

"Progress in Parotid Surgery."
Robert E. Boswell, Dayton, O.

"Cystadenolymphomas of the Parotid Gland."
John F. Daly, M.D., New York City.
Open Discussion.

"Experience with Trans-Septal-Sphenoid Subtotal Hypophysectomy in Advanced Breast Cancer."
Walter E. Heck, M.D.; Robert C. McNaught, M.D.; Leonard G. Dobson, M.D., (by invitation); and Francis S. Greenspan, M.D., (by invitation), all of San Francisco, Calif.
Open Discussion.

"The Problem of Sinusitis in Children."
Victor R. Alfaro, M.D., Washington, D. C.
Open Discussion.

"Endocrine Aspects of Meniere's Disease."
George E. Shambaugh, Jr., M.D., Chicago, Ill.
Open Discussion.

"Cholesteatoma of the External Auditory Canal."
Lester A. Brown, M.D., Atlanta, Ga.
Open Discussion.

"The Diagnosis and Treatment of Facial Paralysis, Secondary to Basal Skull Fracture."
Miles L. Lewis, Jr., M.D., New Orleans, La.
Open Discussion.

"Temporary Obstruction of the Arterial Supply of the Labyrinth."
Henry Perlman, M.D., Chicago, Ill.
Open Discussion.

"Otolaryngologic Aspects of Cerebrovascular Disease."
Bruce Proctor, M.D., Detroit, Mich.
Open Discussion.

"Juvenile Nasopharyngeal Angiofibroma."
Maurice Schiff, M.D., Oakland, Calif.
Open Discussion.

"Late Hearing Results in Mobilization Surgery."
Samuel Rosen, M.D., New York City, and
Clair M. Kos, M.D., Iowa City, Ia.
Open Discussion.

"Trends in Mobilization Surgery."
Howard P. House, M.D., Los Angeles, Calif.

UNIVERSITY OF MICHIGAN MEDICAL CENTER.

The annual Otolaryngology Conference at the University of Michigan will be held April 16, 17 and 18, 1959, under the direction of Dr. James H. Maxwell, Chairman of the Department of Otolaryngology.

Applications may be addressed to the Department of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.

PROGRAM OF THE NINETY-SECOND ANNUAL MEETING OF THE AMERICAN OTOLOGICAL SOCIETY.

Hot Springs, Va., March 13-14, 1959.

The Cochlear Potentials and Their Relation to Hearing.
E. Glen Wever, Ph.D.

More About the Physiology of the Cochlea.
Hallowell Davis, M.D.

Audiometry by Electroencephalography.
A. J. Derbyshire, M.D. (by invitation).

Ototoxicity of Kanamycin.
J. E. Hawkins, Jr., Ph.D. (by invitation).

A Cause of Sudden Deafness.
William Saunders, M.D. (by invitation).
William Libby, M.D. (by invitation).

Acoustic Trauma Following Intermittent Exposure to Tones and Noise.
Walter Covell, M.D. (by invitation).
Don Eldredge, M.D. (by invitation).

An Experimental Study of the Dynamic Circulation of the Labyrinthine Fluids of Living Mammals.
Francis L. Welle, M.D.;
John W. Irwin, M.D. (by invitation).
Coza Jako, M.D. (by invitation).
Patricia Palmer, A.B. (by invitation).

Long Term Results from Surgery for Otosclerosis.
Theodore E. Walsh, M.D.

Ultra-Sonic Therapy of Meniere's Disease.
Franz Altmann, M.D.

Presbycusis.
Edmund P. Fowler, M.D.

Nihil Sub Sole Novum.
Lyle Sellers, M.D.

Otic Embryopathy.
George Kelemen, M.D.

Cochlear Blood Flow in Hypothermia.
H. B. Perlman, M.D.;
Robert Butler, M.D., and
Robert Kimura (by invitation).

Postural Mystagmus Produced by Cerebellar Lesions in the Cat.
Cesar Fernandez, M.D. (by invitation).

Fluid Ears and Nerve Deafness, Circa 1835.
Gordon Hoople, M.D.
Wesley H. Bradley, M.D. (by invitation).

Tympanoplasty.
Fred Guilford, M.D.

Surgical Treatment of Facial Paralysis and Associated Conductive Deafness in Fracture of the Temporal Bone.
H. E. McHugh, M.D.

POSTGRADUATE MEDICAL INSTRUCTION DEPARTMENT—THE MOUNT SINAI HOSPITAL.

An intensive Course in Rhinoplasty, Reconstructive Surgery of the Nasal Septum and Otoplasty will be given July 11, to July 24, 1959, by Dr. Irving B. Goldman and staff at the Mount Sinai Hospital in affiliation with Columbia University.

Candidates for the Course should apply to Registrar for Postgraduate Medical Instruction, The Mount Sinai Hospital, Fifth Avenue and 100th Street, New York 29, New York.

DIRECTORY OF OTOLARYNGOLOGIC SOCIETIES.

(Secretaries of the various societies are requested to keep this information up to date).

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Erling W. Hansen, 90 So. Ninth St., Minneapolis, Minn.
Executive Secretary: Dr. William L. Benedict, Mayo Clinic, Rochester, Minn.
Meeting: Palmer House, Chicago, Ill., Oct. 10-15, 1959.

AMERICAN BOARD OF OTOLARYNGOLOGY.

AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION.

President: Dr. Francis W. Davison, Geisinger Memorial Hospital, Danville, Pa.
Vice-President: Dr. George S. McReynolds, 615 N. Boulevard, Galveston, Tex.
Secretary: Dr. F. Johnson Putney, 1712 Locust St., Philadelphia 3, Pa.
Treasurer: Dr. Verling K. Hart, 106 W. 7th St., Charlotte, N. C.
Meeting: The Homestead, Hot Springs, Va., March 10-11, 1959.

AMERICAN LARYNGOLOGICAL ASSOCIATION.

President: Dr. Fred W. Dixon, Cleveland, Ohio.
Secretary: Dr. James H. Maxwell, Ann Arbor, Mich.
Treasurer: Dr. Francis E. LeJeune, New Orleans, La.
Editor, Historian, and Librarian: Dr. Edwin N. Broyles, Baltimore, Md.
Meeting: The Homestead, Hot Springs, Va., March 8-9, 1959.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. Gordon Hoople, 1100 E. Genesee St., Syracuse 10, N. Y.
President-Elect: Dr. Theo. E. Walsh, 640 So. Kingshighway, St. Louis 10, Mo.
Secretary: Dr. C. Stewart Nash, 700 Medical Arts Bldg., Rochester 7, N. Y.
Annual Meeting: The Homestead, Hot Springs, Va., March 10-11-12, 1959. (Mornings only).

Meetings of the Sections:

Eastern: Savoy Plaza, New York, N. Y., January 8-9, 1959.
Council: Savoy Plaza, New York, N. Y., January 10, 1959.
Middle: Park Plaza Hotel, St. Louis, Mo., January 12-13, 1959.
Western: The Ahwahnee Hotel, Yosemite Valley, Calif., January 17-18, 1959.
Southern: Academy of Medicine, Hotel Atlanta Biltmore, Atlanta, Ga., January 23-24, 1959.

AMERICAN MEDICAL ASSOCIATION, SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY.

Chairman: Dr. Victor R. Alfaro, Washington, D. C.
Vice-Chairman: Dr. Harold F. Schuknecht, Detroit, Mich.
Secretary: Dr. Walter E. Heck, San Francisco, Calif.
Representative to Scientific Exhibit: Dr. Walter H. Maloney, Cleveland, Ohio.
Section Delegate: Dr. Gordon F. Harkness, Davenport, Ia.
Alternate Delegate: Dr. Dean M. Lierle, Iowa City, Ia.
Meeting: Atlantic City, June 8-12, 1959.

AMERICAN OTOLOGICAL SOCIETY, INC.

President: Dr. Moses Lurie, Boston, Mass.
President-Elect: Dr. R. C. Martin.
Secretary: Dr. Lawrence R. Boies, University Hospitals, Minneapolis 14, Minn.
Meeting: The Homestead, Hot Springs, Va., March 13-14, 1959.

AMERICAN OTORHINOLOGIC SOCIETY FOR THE ADVANCEMENT OF PLASTIC AND RECONSTRUCTIVE SURGERY.

President: Dr. Joseph Gilbert, 111 E. 61st St., New York, N. Y.
Vice-President: Dr. Kenneth Hinderer, 402 Medical Arts Bldg., Pittsburgh, Pa.
Secretary: Dr. Louis Joel Feit, 66 Park Ave., New York 16, N. Y.
Treasurer: Dr. Arnold L. Caron, 36 Pleasant St., Worchester, Mass.

AMERICAN RHINOLOGIC SOCIETY.

President: Dr. Russell I. Williams, 408 Hynds Bldg., Cheyenne, Wyo.
Secretary: Dr. Robert M. Hansen, 1735 No. Wheeler Ave., Portland, Ore.
Annual Clinical Session: Illinois Masonic Hospital, Chicago, Ill., October, 1958.
Annual Meeting:

AMERICAN SOCIETY OF FACIAL PLASTIC SURGERY.

President: Dr. Trent W. Smith, 327 East State St., Columbus 15, Ohio.
Vice-President: Dr. Oscar J. Becker, Chicago, Ill.
Secretary: Dr. Samuel M. Bloom, 123 East 83 St., New York 28, N. Y.
Meeting: New York, N. Y., March 18 and July 15, 1959.

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY.

President: Dr. Joseph W. Hampsey, Grant Bldg., Pittsburgh 19, Pa.
Secretary-Treasurer: Dr. Daniel S. DeStio, 121 S. Highland Ave., Pittsburgh 6, Pa.
Annual Meeting:

ASSOCIACAO MEDICA DO INSTITUTO PENIDO BURNIER—CAMPINAS.

President: Dr. Antonio Augusto de Almeida.
First Secretary: Dr. Alberto Galo.
Second Secretary: Dr. Alfredo Porto.
Librarian-Treasurer: Dr. L. de Souza Queiroz.
Editors for the Archives of the Society: Dr. J. Penido Burnier, Dr. Guedes de Melo Filho and Dr. Roberto Franco do Amaral.
Meetings: Twice every month, first and third Thursdays, 8:30 P.M.

ASOCIACION DE OTORRINOLARINGOLOGIA Y BRONCOESOFAGOLOGIA DE GUATEMALA.

Presidente: Dr. Julio Quevedo, 15 Calle Oriente No. 5.
First Vice-Presidente: Dr. Héctor Cruz, 3a Avenida Sur No. 72.
Second Vice-Presidente: Dr. José Luis Escamilla, 5a Calle Poniente No. 48.
Secretario-Tesorero: Dr. Horace Polanco, 13 Calle Poniente No. 9-D.

ASOCIACION DE OTO-RINO-LARINGOLOGIA DE BARCELONA, SPAIN.

Presidente: Dr. J. Abello.
Vice-Presidente: Dr. Luis Sufie Medan.
Secretario: Dr. Jorge Perellò, 319 Provenza, Barcelona.
Vice-Secretario: Dr. A. Pinart.
Vocal: Dr. J. M. Ferrando.

BALTIMORE NOSE AND THROAT SOCIETY.

Chairman: Dr. Walter E. Loch, 1039 No. Calvert St., Baltimore, Md.
Secretary-Treasurer: Dr. Theodore A. Schwartz.

BUENOS AIRES CLUB OTOLARINGOLOGICO.

Presidente: Dr. K. Segre.
Vice-Presidente: Dr. A. P. Belou.
Secretario: Dr. S. A. Aranz.
Pro-Secretario: Dr. J. M. Tato.
Tesorero: Dr. F. Games.
Pro-Tesorero: Dr. J. A. Bello.

CANADIAN OTOLARYNGOLOGICAL SOCIETY SOCIETE CANADIENNE D'OTOLARYNGOLOGIE.

President: Dr. Robert T. Hayes, 42 Cobourg St., St. John, N. B.
Secretary: Dr. Donald M. McRae, 324 Spring Garden Rd., Halifax, N. S.
Meeting: Sheraton-Brock Hotel, Niagara Falls, Ont., Oct. 9-10, 1959.

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. G. C. Otrich, Belleville, Ill.
President-Elect: Dr. Phil R. McGrath, Peoria, Ill.
Secretary-Treasurer: Dr. Alfred G. Schultz, Jacksonville, Ill.

CHICAGO LARYNGOLOGICAL AND OTOLOGICAL SOCIETY.

President: Dr. Stanton A. Friedberg, 122 So. Michigan Ave., Chicago 3, Ill.
Vice-President: Dr. Maurice Snitman, 408 So. 5th Ave., Maywood, Ill.
Secretary-Treasurer: Dr. Fletcher Austin, 700 No. Michigan Ave., Chicago 11, Ill.
Meeting: First Monday of each month, October through May.

CHILEAN SOCIETY OF OTOLARYNGOLOGY.

President: Dr. Enrique Grünwald S.
Vice-President: Dr. Agustin Estartus.
Secretary: Dr. Marcos Chaimovich S.
Treasurer: Dr. Benjamin Kapkan K.
Director: Dr. Alberto Basterrica A.

COLORADO OTOLARYNGOLOGY SOCIETY.

President: Dr. James T. Blair, Denver, Colo.
Vice-President: Dr. James Rigg, Grand Junction, Colo.
Secretary: Dr. Will P. Pirkey, Denver, Colo.

DALLAS ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Edward A. Newell.
Vice-President: Dr. Thomas M. McCrory.
Secretary-Treasurer: Dr. James L. Baldwin, 1627 Medical Arts Bldg., Dallas, Tex.

FEDERACION ARGENTINA, DE SOCIEDADES DE OTORRINOLARINGOLOGIA.

Secretary of the Interior: Prof. Dr. Atilio Viale del Carril.
Secretary of the Exterior: Dr. Aldo G. Remorino.
Secretary Treasury: Prof. Dr. Antonio Carrascosa.
Pro-Secretary of the Interior: Prof. Dr. Carlos P. Mercandino.
Pro-Secretary of the Exterior: Prof. Dr. Jaime A. del Sel.
Pro-Secretary of the Treasury: Dr. Jorge Zubizarreta.

FIRST CENTRAL AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY.

President: Dr. Victor M. Noubleau, San Salvador.
Secretary-Treasurer: Dr. Hector R. Silva, Calle Arce No. 84, San Salvador, El Salvador, Central America.

FLORIDA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Edson J. Andrews.
President-Elect: Dr. G. Dekle Taylor.
First Vice-President: Dr. Kenneth S. Whitmer.
Second Vice-President: Dr. William H. Anderson, Jr.
Secretary-Treasurer: Dr. Joseph W. Taylor, Jr.

FOURTH LATIN-AMERICAN CONGRESS OF OTORINOLARINGOLOGIA.

President: Dr. Dario.
Secretary:
Meeting:

FORT WORTH EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. Van D. Rathgeber.
Vice-President: Dr. William Skokan.
Secretary-Treasurer: Dr. Paul Rockwell.

GREATER MIAMI EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. William B. Steinman.
President-Elect: Dr. James H. Mendel, Jr.
Secretary-Treasurer: Dr. H. Carlton Howard.
Meeting quarterly (March , May, October and December), on the second Thursday of the month, 6:30 P.M., at Urmey Hotel, Miami.

INTERNATIONAL BRONCHOESOPHAGOLOGICAL SOCIETY.

President: Dr. Jo Ono, Tokyo, Japan.
Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting: Eighth International Congress of Bronchoesophagology, Mexico City, March 14-18, 1959.

KANSAS CITY SOCIETY OF OTOLARYNGOLOGY AND OPHTHALMOLOGY.

President: Dr. Clarence H. Steele.
President-Elect: Dr. Dick H. Underwood.
Secretary: Dr. James T. Robison, 4620 J. C. Nichols Parkway, Kansas City, Mo.
Meeting: Third Thursday of November, January, February and April.

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Max E. Pohlman.
Secretary-Treasurer: Dr. Wendell C. Irvine.
Chairman of Ophthalmology Section: Dr. Carroll A. McCoy.
Secretary of Ophthalmology Section: Dr. Philip D. Shanedling.
Chairman of Otolaryngology Section: Dr. Robert W. Godwin.
Secretary of Otolaryngology Section: Dr. Francis O'N. Morris.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd., Los Angeles, Calif.
Time: 6:30 P.M. last Monday of each month from September to June, inclusive—Otolaryngology Section. 6:30, first Thursday of each month from September to June, inclusive—Ophthalmology Section.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY.

President: Dr. Fred D. Hollowell, Lamar Life Bldg., Jackson, Miss.
Secretary: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.
Meeting: Edgewater Gulf Hotel, Edgewater Park, Miss., May 15-16, 1959.

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Chairman: Members serve as chairmen in alphabetical order monthly.
Secretary-Treasurer: Dr. Roland H. Myers, 1720 Exchange Bldg., Memphis, Tenn.
Assistant Secretary-Treasurer: Dr. William F. Murrah, Jr., Exchange Bldg., Memphis, Tenn.
Meeting: Second Tuesday in each month at 8:00 P.M. at Memphis Eye, Nose and Throat Hospital.

MEXICAN ASSOCIATION OF PLASTIC SURGEONS.

President: Dr. Cesar LaBoide, Mexico, D. F.
Vice-President: Dr. M. Gonzales Ulloa, Mexico, D. F.
Secretary: Dr. Juan De Dios Peza, Mexico, D. F.

MEXICAN SOCIETY OF OTOLARYNGOLOGY.

President: Dr. Rafael Giorgana.
Secretary: Dr. Carlos Valenzuela, Monterey 47, Mexico 7, D. F.

MISSISSIPPI VALLEY MEDICAL SOCIETY.

President: Dr. Arthur S. Bristow, Princeton, Mo.
Secretary-Treasurer: Dr. Harold Swanberg, Quincy, Ill.
Assistant Secretary-Treasurer: Dr. Jacob E. Reisch, Springfield, Ill.

NETHERLANDS SOCIETY OF OTO-RHINO-LARYNGOLOGY.
(Nederlandsche Keel-Neus-Oorheelkundige Vereeniging.)

President: Dr. H. Navis, Sonsbeekweg 6, Arnhem.
Secretary: Dr. W. H. Struben, J. J. Viottastraat 1, Amsterdam.
Treasurer: Mrs. F. Velleman-Pinto, Jac. Ohrechtstr. 66, Amsterdam.

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. J. C. Peele, Kinston Clinic, Kinston, N. C.
Vice-President: Dr. George E. Bradord, Winston-Salem, N. C.
Secretary-Treasurer: Dr. J. D. Stratton, 1012 Kings Drive, Charlotte 7, N. C.
Meeting:

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.

President: Mr. G. L. Thompson, 16 Ramshill Road, Scarborough, Yorkshire.
Vice-President: Mr. J. H. Otty, Frizley Old Hall, Frizinghall Road, Bradford, Yorkshire.
Secretary and Treasurer: Mr. R. Thomas, 27 High Petergate, York, Yorkshire.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. David D. DeWeese, 1216 S. W. Yamhill St., Portland 5, Ore.
Secretary-Treasurer: Dr. Paul B. Myers, 223 Medical Dental Bldg., Portland 5, Ore.
Meeting: Fourth Tuesday of each month from September through May, Henry Thiele Restaurant, 23rd and W. Burnside, Portland, Ore.

OTOSCLEROSIS STUDY GROUP.

President: Dr. E. P. Fowler, Jr., 180 Fort Washington Ave., New York 32, New York.
Secretary-Treasurer: Dr. Arthur L. Juers, 1018 Brown Building, Louisville 2, Ky.
Meeting: Palmer House, Chicago, Ill., October 11, 1959.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY.

President: Dr. H. Leroy Goss, 620 Cobb Bldg., Seattle 1, Washington.
Secretary-Treasurer: Dr. Homer E. Smith, 508 East South Temple, Salt Lake City, Utah.
Meeting:

PAN AMERICAN ASSOCIATION OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY.

President: Dr. Paul Holinger, 700 No. Michigan Blvd., Chicago, Ill.
Executive Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting: Seventh Pan American Congress of Oto-Rhino-Laryngology and Broncho-Esophagology.
Time and Place: Miami, Fla., March, 1960.

PHILADELPHIA LARYNGOLOGICAL SOCIETY.

President Dr. John J. O'Keefe.
Vice-President: Dr. Joseph P. Atkins.
Secretary: Dr. William A. Lell.
Executive Committee: Dr. Harry P. Schenck, Dr. Benjamin H. Shuster, Dr. William A. Lell, Dr. William J. Hitschler, and Dr. Chevalier L. Jackson.

PITTSBURGH OTOLOGICAL SOCIETY.

President: Dr. Bernard L. Silverblatt, 3500 Fifth Avenue, Pittsburgh, Pa.
Vice-President: Dr. Emory A. Rittenhouse, 203 Masonic Bldg., McKeesport, Pa.
Secretary-Treasurer: Dr. John T. Dickinson, Mercy Hospital, Pittsburgh 19, Pa.

PORTUGUESE OTORHINOLARYNGOLOGICAL SOCIETY.

President: Dr. Albert Luis de Mendonca.
Secretary: Dr. Antonio da Costa Quinta, Avenida, de Liberdale 65, 1° Lisbon.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Clifton E. Benson, Bremerton, Wash.
President-Elect: Dr. Carl D. F. Jensen, Seattle, Wash.
Secretary: Dr. Willard F. Goff, 1215 Fourth Ave., Seattle, Wash.

RESEARCH STUDY CLUB OF LOS ANGELES, INC.

Chairman: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.
Treasurer: Dr. Norman Jesberg, 500 So. Lucas Ave., Los Angeles 17, Calif.
Otolaryngology: Dr. Russell M. Decker, 65 N. Madison Ave., Pasadena 1, Calif.
Ophthalmology: Dr. Warren A. Wilson, 1930 Wilshire Blvd., Los Angeles 57, Calif.
Mid-Winter Clinical Convention annually, the last two weeks in January at Los Angeles, Calif.

SECTION OF OTOLARYNGOLOGY OF THE MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA.

Chairman: Dr. J. L. Levine.
Vice-Chairman: Dr. Russell Page.
Secretary: Dr. James J. McFarland.
Treasurer: Dr. Edward M. O'Brien.
Meetings are held the second Tuesday of September, November, January, March and May, at 6:30 P.M.
Place: Army and Navy Club, Washington, D. C.

SCOTTISH OTOLARYNGOLOGICAL SOCIETY.

President: Dr. F. T. Land, 13 Newton Place, Glasgow, C. 3.
Secretary-Treasurer: Dr. J. F. Birrell, 14 Moray Place, Edinburgh.
Assistant Secretary: Dr. H. D. Brown Kelly, 11 Sandyford Place, Glasgow, C. 3.

SOCIEDAD COLUMBIANA DE OFTALMOLOGIA Y OTORRINOLARINGOLOGIA (BOGOTA, COLUMBIA).

Presidente: Dr. Alfonso Tribin P.
Secretario: Dr. Felix E. Lozano.
Tesorero: Dr. Mario Arenas A.

SOCIEDAD CUBANA DE OTO-LARINGOLOGIA.

President: Dr. Reinaldo de Villiers.
Vice-President: Dr. Jorge de Cárdenas.
Secretary: Dr. Pablo Hernandez.

SOCIEDAD DE ESTUDIOS CLINICOS DE LA HABANA.

Presidente: Dr. Frank Canosa Lorenzo.
Vice-Presidente: Dr. Julio Sanguily.
Secretario: Dr. Juan Portuondo de Castro.
Tesorero: Dr. Luis Ortega Verdes.

SOCIEDAD DE OTORRINOLARINGOLOGIA Y BRONCOESOFAGOSCOPIA DE CORDOBA.

Presidente: Dr. Aldo Remorino.
Vice-Presidente: Dr. Luis E. Olsen.
Secretario: Dr. Eugenio Romero Diaz.
Tesorero: Dr. Juan Manuel Pradales.
Vocales: Dr. Osvaldo Suárez, Dr. Nondier Asis R., Dr. Jorge Bergallo Yofre.

SOCIEDAD DE OTO-RINO-LARINGOLOGIA, COLEGIO MEDIO DE EL SALVADOR, SAN SALVADOR, C. A.

President: Dr. Salvador Mixco Pinto.
Secretary: Dr. Daniel Alfredo Alfaro.
Treasurer: Dr. Antonio Pineda M.

SOCIEDAD ESPANOLA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. D. Adolfo Hinojar Pons.
Vice-Presidente: Dr. D. Jose Perez Mateos.
Secretario General: Dr. D. Francisco Marafiés.
Tesorero: Dr. D. Ernesto Alonso Ferrer.

SOCIEDAD MEXICANA DE OTORRINOLARINGOLOGIA

Monterrey 47-201
Mexico 7, D. F.

President: Dr. Rafael Giorgana.
Secretary: Dr. Carlos Valenzuela.
Treasurer: Dr. Benito Madariaga.
First Vocal: Dr. Rafael González.
Second Vocal: Dr. Juan Oberhauser.

SOCIEDAD NACIONAL DE CIRUGIA OF CUBA.

Presidente: Dr. Reinaldo de Villers.
Vice-Presidente: Dr. César Cabrera Calderin.
Secretario: Dr. José Xirau.
Tesorero: Dr. Alfredo M. Petit.
Vocal: Dr. José Gross.
Vocal: Dr. Pedro Hernández Gonzalo.

SOCIEDAD OTO-RINO-LARINGOLOGIA DE LOS HOSPITALES DE MADRID.

Presidente: Dr. Don Fernando Beltrán Castillo.
Secretario General: Dr. Don Alfonso Vassallo de Mumbert.
Tesorero: Dr. Don Rafael Garcia Tapia.

SOCIEDAD VENEZOLANA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. Gabriel Briceño Romero.
Vice-Presidente: Dr. Silvestre Rincón Fuenmayor.
Secretario General: Dr. Oscar Bustamante Miranda.
Tesorero: Dr. Arturo Marrero Gómez.
Vocales: Dr. Miguel Octavio Russa, Dr. Benjamin Briceño, Dr. Oscar Gonzalez Castillo.

SOCIEDADE DE OFTALMOLOGIA E OTORRINOLARINGOLOGIA DO RIO GRANDE DO SUL.

President: Dr. Paulo Fernando Esteves.
Vice-President: Dr. Jayme Schilling.
First Secretary: Dr. Carlos Buede.
Second Secretary: Dr. Moizés Sabani.
First Treasurer: Dr. Israel Scherman.
Second Treasurer: Dr. Rivadávia C. Meyer.
Librarian: Dr. Carlos M. Carrion.

SOCIEDAD PANAMENA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. Manuel Preciado.
First Vice-Presidente: Dr. Alonso Roy.
Second Vice-Presidente: Dr. Carlos Arango Carbone.
Secretario: Dr. Maria Esther Villalaz.
Tesorero: Dr. Ramòn Crespo.

SOCIEDADE PORTUGUESA DE OTORRINOLARINGOLOGIA E DE BRONCO-ESOFAGOLOGIA.

Presidente: Dr. Alberto Luis De Mendonca.
Vice-Presidente: Dr. Jaime de Magalhaes.
1.° Secretario: Dr. Antonio da Costa Quinta.
2.° Secretario: Dr. Albano Coelho.
Tesoureiro: Dr. Jose Antonio de Campos Henriques.
Vogais: Dr. Teofilo Esquivel.
Dr. Antonio Cancela de Amorim.
Sede: Avenida da Liberdade, 65, 1°, Lisboa.

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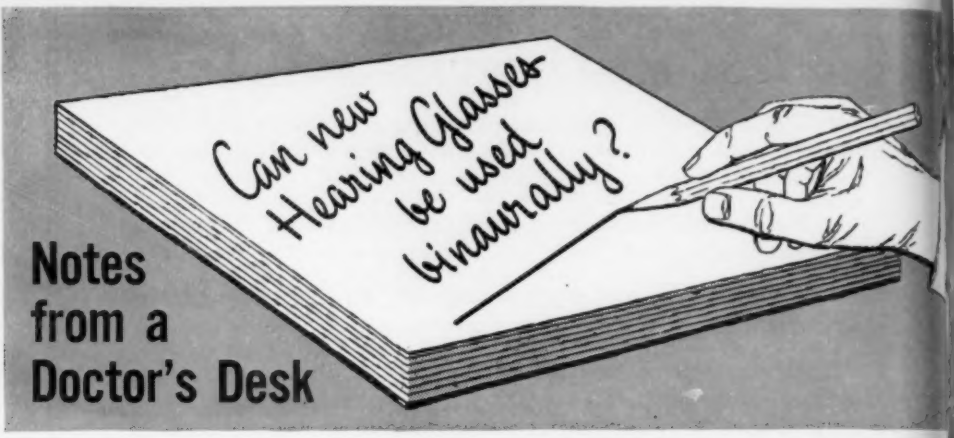

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